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CONTENTS

NUMBER 1, FEBRUARY, 1945

Lymphogranuloma venereum. HERBERT KOTEEN.....	1
The Late Effects of Cerebral Birth Injuries. CLEMENS E. BENDA.....	71

NUMBER 2, MAY, 1945

Diabetic Neuropathy. General Review with Report of 125 Cases. R. WAYNE RUNDLES.....	111
Histopathology of the Central Nervous System after Exposure to High Altitudes, Hypoglycemia and Other Conditions Associated with Central Anoxia. E. C. HOFF, R. G. GRENELL AND J. F. FULTON.....	161

NUMBER 3, SEPTEMBER, 1945

Tick Paralysis: a Critical Review. JOHN B. STANBURY AND JAMES H. HUYCK.....	219
The Cutaneous Arterial Spider: A Survey. WILLIAM BENNETT BEAN....	243
The Chemical Separation and the Clinical Appraisal of the Components of the Blood. EDWIN J. COHN.....	333

NUMBER 4, DECEMBER, 1945

Cerebral Injury by Blunt Mechanical Trauma. Review of Literature. C. G. TEDESCHI, M.D.....	339
The Absorption and Elimination of Gases of the Body in Relation to its Fat and Water Content. CAPTAIN A. R. BEHNKE (MC).....	359
Decompression Sickness Incident to Deep Sea Diving and High Altitude Ascent. CAPTAIN A. R. BEHNKE (MC).....	381
Circulation and Respiration in Fever. MARK D. ALTSCHULE AND A. STONE FREEDBERG.....	403

LYMPHOGRANULOMA VENEREUM

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CONTENTS

	PAGE
I. Introduction.....	2
II. Historical Background.....	3
A. Earliest Descriptions.....	3
B. Terminology.....	3
C. Developmental Concepts.....	4
III.	5
B. Age.....	5
C. Sex.....	5
D. Race.....	6
E. Infectiousness.....	6
IV. Clinical Manifestations.....	7
Proved Lesions.....	7
A. Primary Lesions.....	7
B. Inguinal Buboes.....	8
C. Constitutional Reactions.....	8
D. Elephantiasis of External Genitalia.....	9
E. Urethral and Cervical Infections.....	10
F. Anorectal Syndrome.....	11
G. Ocular Involvement.....	11
H. Meningitis.....	12
Unproved Lesions.....	12
I. Ulcerative Colitis.....	13
J. Upper Intestinal Tract Infections.....	13
K. Chronic Salpingitis and Parametritis.....	14
L. Skin and Subcutaneous Tissues.....	14
M. Joint Involvement.....	15
N. Lesions of Head, Neck and Axilla.....	16
O. Urologic Lesions.....	17
Additional Manifestations.....	17
P. Hyperpyrexia.....	17
Q. Pulmonary Infection.....	18
R. Ocular Lesions, Other than Conjunctivitis.....	18
S. Malignant Degeneration.....	18
T. Influence on Reproduction.....	19
U. Association with Other Diseases.....	19
V. Childhood Infections.....	20
W. Immunity.....	20
X. As a Cause of Death.....	20
V. Etiology.....	21
A. Isolation of Causative Agent.....	21
B. Morphology and Developmental Forms.....	21
C. Size.....	22
D. Physical Chemical Properties.....	23

E. Studies in Experimental Animals.....	23
F. Cultivation of the Virus.....	24
G. Toxic Factor.....	25
H. Virulence Studies.....	25
I. Immunologic Studies.....	25
J. Relationship to Other Pathogenic Agents.....	26
VI. Pathology and Pathogenesis.....	28
A. Primary Genital Lesions.....	28
B. Buboes.....	28
C. Probable Pathogenesis of Constitutional Reactions.....	30
D. Elephantiasis of External Genitalia.....	30
E. Rectal Involvement.....	31
VII. Diagnosis.....	32
A. Skin Sensitivity Tests.....	32
B. Complement-Fixation.....	36
C. Inverted Frei Test.....	38
D. Intravenous Frei Reaction.....	38
E. Histopathology.....	38
F. Demonstration of Neutralizing Substances.....	39
G. Isolation of Causative Agent.....	39
H. Conclusions.....	39
VIII. Differential Diagnosis.....	40
A. Diseases Associated with Genital Lesions.....	40
B. Diseases Associated with Inguinal Adenopathy.....	43
IX. Laboratory Findings.....	43
A. Blood.....	43
B. Serologic Tests for Syphilis.....	45
C. Urine.....	45
D. Cerebrospinal Fluid.....	45
E. Stools.....	45
F. X-ray Studies.....	46
X. Treatment.....	46
A. Introduction.....	46
B. Prophylaxis and Isolation.....	46
C. Therapeutic Measures, Excluding Sulfonamides.....	47
D. Experimental Sulfonamide Therapy.....	49
E. Current Therapy of Specific Lesions.....	50
F. Evaluation of Treatment.....	54
XI. Summary.....	54
XII. Bibliography.....	55

I. INTRODUCTION

Lymphogranuloma venereum is a virus disease usually transmitted by venereal contact, and manifested by both generalized constitutional symptoms and localized acute and chronic tissue changes. Although the inguinal variety of the disease had been observed and clearly described over a century ago, medical attention was not directed toward this syndrome as a specific entity until 1913 when Durand, Nicolas and Favre (67) published their monograph. Interest was further accelerated by the introduction of the cutaneous test by Frei (91) in 1925. Since then the discovery of the etiologic agent and finding of successful therapeutic agents have almost wholly clarified the clinical aspects.

II. HISTORICAL BACKGROUND

A. *Earliest Description*

Hunter in 1786 (170) postulated that there are two distinct types of buboes associated with the genital lesions which he ascribed to syphilis. He confused the non-suppurating bubo commonly found during early syphilitic infection with one probably caused by the agent of lymphogranuloma venereum. He observed that "the second are generally preceded and attended with slight fever, or common symptoms of a cold and that the buboes are generally indolent and slow in their progress. When they do suppurate, it is slowly and often in more glands than one. The matter comes slowly to the skin, and the color is different from that of the other (syphilitic bubo), being more purple."

The first comprehensive descriptions of the infection in the inguinal regions may be found in "Treatise on Venereal Disease and its Varieties" by William Wallace, published in 1833 (357). His observations leave little to be added by subsequent investigators. "The skin becomes red and is found to be adherent to the surface of the tumor over which it could be previously moved, even after the tumor had become adherent to the subjacent and surrounding tissues. The bubo then for the most part increases with rapidity, the pain becomes of a throbbing kind; some degree of fever sets in, marked by an acceleration of pulse and increase of heat, loss of appetite, imperfect sleep, with a general feeling of indisposition." In describing the "indolent primary syphilitic bubo," Wallace traces the chronologic progress of the inguinal nodes from first swelling until "the matter slowly approaches to the skin by one extensive surface or at successive times by a number of slower surfaces. In both cases, the vitality of a large portion of integument is often destroyed from whence there results . . . numerous fistulous openings."

Larsen (192) was the first to describe rectal lesions, both proctitis and stricture, which he presumed were due to syphilis. He referred to this syndrome as "hyperplastic infiltration of the rectum."

The earliest description of elephantiasis of the external genitalia in women is recorded by Desruelles (65) in 1844, according to Stannus. The lesions were accompanied by inguinal adenopathy, and in one patient there was evidence of previous suppuration. The name "esthiomène" was assigned to this lesion by Huguier (169) because it is derived from the Greek, "eating or eroding."

Fournier (86) also treated cases of esthiomène in 1873, although it was his impression that the "scleremic-like hardness of the labia majora, which are a sombre rose color, and the vivid red of the labia minora" are due to syphilis. He incorrectly applied the name of "syphilome anorectal" to the anorectal lesions.

The first descriptions of merit from this country were by Klotz (182), who described 120 cases of inguinal adenitis.

B. *Terminology*

Confusion is caused by the fact that this infection is called by a variety of names. The Standard Nomenclature of Diseases uses the term lymphogranu-

loma, venereal. We prefer the expression *Lymphogranuloma venereum* which appears most frequently in the literature and is used throughout this paper. Godding (108) in 1896 referred to the enlarged nodes as "climatic buboes." Klotz (182) used the expression "Strumosen Bubonene." Durand, Nicolas and Favre (67) believed the lesions related to Hodgkin's disease because of the microscopic picture, hence referred to them as "lymphogranulomatose inguinale subaigue." Stannus (339) in England termed the inguinale lesions "lymphogranuloma inguinale," and Sulzberger (346) called the lesions "lymphopathia venereum." Phillips (270) used the expression "tropical bubo." Kolmer (185) found, in addition to the above, the following terminology used in the literature: venereal lymphogranuloma, lymphogranuloma inguinale venereum, granulomatosis lymphatosis, non-tuberculosis granuloma, pudendal ulcer.

This disease should be differentiated from granuloma inguinale, a disease of the skin in the inguinal region, associated with the presence of Donovan bodies.

C. Developmental Concepts

Although adequate descriptions of the inguinal buboes, elephantiasis of the genitalia, anorectal lesions and systemic reactions appeared in the world literature, it was not until after clinical application of the cutaneous test of Frei that these entities were realized to be initiated by the same agent.

In 1925 Frei (91) obtained some pus from a patient with bilateral inguinal adenitis, and after preliminary preparation injected it intra-cutaneously into patients with enlarged nodes. These patients included some with tuberculosis, syphilis, suppurative anerobic organisms, leukemia, and Hodgkin's disease. Only those with the lesions similar to the donor of the pus developed a papule at the site of the inoculation. All the others were negative.

In 1928 Frei and Koppel (99) observed that patients with anorectal involvement and esthiomène, hitherto believed to have syphilis, had positive skin reactions with the buo-pus antigen. Direct proof that these lesions are incited by the same etiologic agent came with recovery of the virus from the genitalia by Koch (184) and from the anorectal tissue by Ravaut, Levaditi, Lambling and Cachera (292).

Goodman (109) suspected that some cases of colitis as well as proctitis were caused by this agent, and Paulson (261) has extended this work to include a small group of patients with idiopathic ulcerative colitis.

Since 1930, when Helleström and Wassén (156) reported a method for isolating the causative agent, previously unexplained inflammatory reactions have been re-studied. It is now evident that lymphogranuloma venereum is not only a disease of the genital area, but is a protean disease with numerous manifestations.

Frei (96) recently described the developmental phases in four steps:

1. Proof by Durand, Nicolas and Favre that strumous bubo is a separate venereal disease, (67).
2. Discovery of a specific skin test by Frei. This permitted the identification of climatic bubo, rectal stricture and esthiomène as the same disease, (93), (99).

3. Transmission of the disease to animals by Helleström and Wassén by intracerebral inoculation of monkeys, (156).
4. Experimental study of the disease as a virus infection.

III. EPIDEMIOLOGY

A. Geographic Distribution

Numerous reports testify to the worldwide distribution of lymphogranuloma venereum. It is especially prevalent in tropical and subtropical countries, but cases have been observed throughout Europe and North and South America.

In 1933 Hellström and Wassén (158) sent out questionnaires throughout the world and collected 1800 cases from 350 clinics. Since then the infection has been reported from new areas. This suggests, not so much an apparent increase in the disease, as a growing awareness that it exists. This premise is supported by additional data acquired by Favre and Hellström (74) in 1939 when a second survey brought data from 115 clinics solicited. There were 10,000 cases reported from every country in Europe, and parts of North and South America, Java, India and the Far East. It was the impression of the authors that this represents not an increase in frequency but that "one has seldom learned to recognize it, until recently."

There have been detailed reports from England (76), Ireland (277), France (257), Germany (98), Italy (8), Spain (12), (13), Czechoslovakia (174), Sweden (158), Norway (363), Indo-China (354), Dutch East Indies (21), China and Japan (127), (358), Belgian Congo (33), Tanganyika (124), Algiers (193), Morocco (251), Australia (274), Chile (43), Argentina (369), Brazil (52), Venezuela (14), Uruguay (143), Mexico (314), Porto Rico (159), India (280), and Rumania (172).

The disease has been seen frequently throughout the United States. In 1939, D'Aunoy and von Haam (59) reported the existence of the infection in twenty-seven states. It is especially common along the eastern seaboard and in the South, and uncommon in the New England States (168).

B. Age

The incidence of any venereal disease is greatest during the period of sexual activity. The rectal lesions are seen in an older age group because these lesions usually require several years to attract clinical attention. Reports of infection of children have appeared in the pediatric literature.

C. Sex

It is likely that the incidence of any venereal disease is approximately equal in members of both sexes. The superficial inguinal node involvement is relatively uncommon in women during the acute stage of infections. It is for this reason that men are usually seen at an earlier age than women. On the other hand esthiomène and rectal involvement, which are essentially late lesions, are frequently the first evidence of infection in women.

D. Race

Since the disease is spread primarily by sexual contact, it is found most commonly among persons whose economic and sociologic status encourages sexual promiscuity. Estimates of the incidence of lymphogranuloma venereum are usually based on the routine Frei or complement-fixation testing of different population groups, usually drawn from out-patient departments of large hospitals and often from venereal disease clinics. In such highly selected samples it appears that in urban areas of the temperate zone, from 20 to 40 per cent of Negroes and from 2 to 5 per cent of white patients are, or have at one time been, infected. In St. Louis (129) 40 per cent of colored and 3.5 per cent of the white patients were found to have positive skin reactions. Using the same test in New Orleans, D'Aunoy and von Haam (59) obtained positive results in 17.4 per cent of colored patients who applied for general medical care. In New York City, Shaffer and others (327) found that in one venereal disease clinic group, all of sixteen colored patients and twenty-seven of thirty-seven white patients tested had positive reactions with the complement-fixation test.

In most persons reacting positively to these tests, there is no history of such infection and no physical evidence of the disease. Assuming that the diagnostic tests in question are valid, infection with the virus of lymphogranuloma venereum is even more prevalent than syphilitic infection, but in the majority of instances the former remains latent without producing any evidence of tissue damage.

E. Infectiousness

Sufficient evidence exists to warrant the conclusion that the agent of lymphogranuloma venereum is readily transmitted to the human host.

1. *Spread by sexual contact:* In one study it was possible to trace the infection in a group of men directly to four prostitutes with whom the men had been consorting. The men were found to have early lesions, although the women had no apparent manifestations. Numerous examples of infection of the head and neck following perverted sexual exposures are described in the section on "Clinical Manifestations." The prevalence of positive skin reactions among population groups known to be sexually promiscuous would appear to justify the opinion that the disease is spread with ease.

2. *Spread by close association:* Of the several examples of this disease cited in the pediatric literature, in none is there evidence of sexual exposure. In Sonck's cases, it is believed that common use of an enema tip was responsible, and, in the cases described by Lujan and Rotter (218), close contact among sisters seemed to be the cause. In some instances it was believed that occupying the same bed was adequate cause for infection.

3. *Spread by direct inoculation:* The first example of this kind (182) occurred when a physician who was excising inguinal buboes inadvertently cut himself with a contaminated scalpel. He developed lymphangitis and axillary lymphadenopathy. Other similar cases have occurred.

4. *Spread among laboratory workers:* Three cases of infection among technicians are reported by Harrop and his associates (147), and another case of eye infec-

tion by Oliphant and his group (259). It is apparent that the handling of the virulent material is not without danger.

IV. CLINICAL MANIFESTATIONS OF LYMPHOGRANULOMA VENEREUM

It is convenient to divide the clinical manifestations of this disease into two groups: those proved to be due to lymphogranuloma venereum by recovery of the causative agent from the lesion; and those suspected of being due to this disease. These are tabulated in Table 1.

Proved Lesions

A. Primary Genital Lesions. There are several types; the most common is the herpetiform variety. The ulcer or "chancie" is seen less frequently and is usually not more than five or six millimeters in size, although larger lesions are

TABLE 1

Clinical manifestations attributed to the virus of lymphogranuloma venereum

LESIONS FROM WHICH THE VIRUS HAS BEEN RECOVERED	LESIONS FROM WHICH THE VIRUS HAS NOT BEEN RECOVERED
1 Primary genital lesions 2 Inguinal buboes 3 Esthomiène 4 Urethritis 5 Cervicitis 6 Anorectal Syndrome 7 Conjunctivitis 8 Meningitis	<p><i>Supporting evidence is good</i></p> 1 Ulcerative colitis 2 Scleritis and parametritis 3 Dermatologic manifestations 4 Joint and bone infections 5 Cervical and axillary adenitis 6 Tongue and lip "chancres" <p><i>Supporting evidence is circumstantial</i></p> 7 Pharyngitis and tonsillitis 8 Enteritis 9 Ocular lesions other than conjunctivitis

occasionally seen in women (Fig 1). In the male the primary lesion usually appears on the coronal sulcus, is painless, transient, evanescent, and heals spontaneously in a few days without scar formation. In the female the site is usually the posterior aspect of the vulva.

Melezer (230) isolated the virus from a barmaid with an acute ulcerative lesion of the external labia by injecting emulsified biopsied material intracerebrally into rabbits who subsequently developed meningo-encephalitis.

Often only a minute lesion is seen and frequently none is demonstrable. In clinical practice the late manifestations of the disease often appear in patients who give no history of a previous genital lesion. In one series the primary lesion was seen only four times in 130 early cases (145).

Stannus (339) describes two additional types of lesions seen uncommonly. The first is a papule 3-4 mm. in diameter, first mentioned by Phylactos (271). The other is a firm nodule 5-10 mm in diameter lying within the tissue of the penis, on its surface a small fistulous opening is found exuding pus.

Occasionally the lesion is located intraurethrally and because of the purulent

discharge, may be confused with acute gonorrhea. On palpating the shaft of the penis a firm mass may be felt; and if repeated smears fail to reveal the presence of Neisserian organisms, and if syphilis can be ruled out, lymphogranuloma should be suspected.

B. Inguinal Bubo. The most frequent manifestation in males is swelling of the inguinal nodes. In 1927 Frei (92) used the intracutaneous test to differentiate lymph node enlargements due to lymphogranuloma virus from other causes, but it was not until the isolation of the agent by Hellerstrom and Wassén (156) that final proof was secured. This was confirmed two years later when Levaditi, Ravaut and Schoen (203) reported transmission of the disease from infected buboes to mice by intracerebral inoculation. Little may be added to the classic descriptions of Wallace (357) quoted in the Historical Introduction.



FIG. 1. PRIMARY LESION OF LYMPHOGRANULOMA ON LEFT LABIUM MAJUS

The most medial nodes are first involved, and infection spreads along the entire inguinal chain. Occasionally, the process recedes spontaneously, but usually terminates in suppuration unless treatment intervenes (Fig. 2).

C. Constitutional Reactions. 1. *Initial Stage:* A generalized systemic reaction is often concurrent with invasion of the inguinal nodes. Symptoms are grippe-like in character, with malaise, headache, fever, arthralgia, myalgia, anorexia, nausea, vomiting, chills and sweats. Epistaxis is reported (107). Backache is not uncommon in women, and D'Aunoy and Schenken (60) suggest that this is associated with iliac and periaortic lymph node invasion. In rare instances, generalized lymphadenopathy is seen (70). In one group (320) of carefully followed patients, 38 of 42 exhibited some fever. In three instances it reached 39.5°C., and preceded the adenitis. Eighteen of the group had an increase in temperature to 38°C. or to 38.5°C. The character of the fever curve is uninfluenced by softening of the lymph nodes or by the appearance of fistulae. A prolonged pyrexia may occur (107) and a relapsing temperature chart is seen uncommonly (35).

2. *Late Stages:* After the initial phase of the disease, most patients enter a

period of latency during which the only evidence of infection is of a laboratory nature. The patient retains cutaneous sensitivity to the antigen, and usually his serum contains the property of fixing complement in the presence of the virus.

In those patients who go on to develop late clinical manifestations of the disease, such as elephantiasis of the external genitalia, or the anorectal syndrome, the constitutional symptoms are variable. The course is similar to that found in any debilitating illness with weakness, weight loss, fatigue, anemia, mental depression and irritability. This picture is especially conspicuous in proctitis with stricture and ulceration.

D. Elephantiasis of the External Genitalia In 1928, Frei and Koppel (99) reported that the enlarged, edematous and violaceous labia previously believed by Fournier (87) to be a lesion of syphilis were actually a late manifestation of lymphogranuloma venereum. These workers observed that five patients with



FIG. 2 UNRUPTURED BILATERAL BUBOES OF LYMPHOGNANULOMA IN A COLORED WOMAN

the anorectal syndrome and esthromène, with an antecedent history of swelling in the inguinal area, gave a positive reaction with the Frei skin antigen. Koch (181) subsequently isolated the agent from infected labial tissue.

Depending on the degree of hyperplasia or necrosis, the genitalia may assume a variety of appearances. There may be elephantiasis with vegetations and polypoid growths (Fig. 3). Fistulae occur frequently, often followed by ulcerations. The lesions may be extremely painful, particularly after tissue destruction begins, and normal functioning of the parts is impossible. The edema may extend from clitoris to anus, and as the infection progresses, tissue breakdown may follow. Stannus (339) refers to one instance in which the anus, perineum, and recto-vaginal septum were destroyed with the formation of a cloaca. The urethra was likewise destroyed, allowing complete extroversion of the bladder. Coutts (10) has recently called attention to elephantiasis of the praeputium of the

clitoris associated with esthiomène. Of 66 prostitutes presenting elephantiasis vulvae, only five had hypertrophy of the clitoris. At first this organ was simply enlarged, but in the absence of treatment the edematous tissue became indurated and finally ulcerated and macerated. The diagnosis was made by the general clinical picture and study of biopsied material.

Elephantiasis of the male external genitalia is uncommon. We recently observed a colored man, age 54, whose penis had become progressively more indurated and disfigured so that urination was both difficult and painful. The Frei test was strongly positive, and although it was believed that extensive fibrosis had taken place, the lesion responded to prolonged sulfathiazole therapy. Netherton and Curtis (255) described a similar case, in which the scrotum was involved. Policaro (272) suggested a causal relationship to plastic induration of the penis, Peyronie's disease, but in three patients that he observed, the Frei test was negative. Midana (237) reported the formation of multiple draining



FIG 3. ELEPHANTIASIS OF EXTERNAL GENITALIA (ESTHIOMÈNE)

sinuses along the dorsum of the penis following inguinal adenitis. Material from these fistulae proved to be effective antigenic material in known Frei reactors.

Elephantiasis of the male external genitalia may follow extirpation of the inguinal buboes (368), after which even gangrene of the scrotum may occur. Enlargement of the external genitalia of both sexes due to lymphogranuloma venereum cannot be distinguished clinically from that due to other causes.

Bubonulus. Recently, Brandt (23) called attention to the formation of circumscribed bubo-like eminences on the penis in a patient who had a history suggestive of this disease and a positive cutaneous reaction. The term "bubonulus" is used to indicate infiltrations about the lymph channels but not including the lymph nodes. The Curths (55) have observed the transition of the small penile lesion of lymphogranuloma venereum into a pigeon-egg sized bubonulus at the same site.

E. Urethral and Cervical Infection. Caminopetros (30) took scrapings from

the urethrae and cervixes of four prostitutes who were strongly Frei positive, but who showed no visible lesions. These women were implicated in transmitting the disease to several men. The emulsified material was inoculated intracerebrally into mice. The brains showed typical lesions, and were antigenic.

Gray (128) describes 25 cases of chronic non-bacterial urethritis with and without ulceration. Some of these women proceeded to stricture formation in spite of various attempts to therapy. All but two of these patients were positive Frei reactors.

F. Anorectal Syndrome. This group of lesions includes proctitis with and without stricture, and also includes lymphorrroids.

1. *Proctitis:* The first symptom of this serious manifestation of infection is rectal bleeding with some purulent discharge. Direct proctoscopic observation reveals inflamed and hyperemic mucosa, with localized denuded areas, in parts of which the mucosa has been replaced by granulation tissue. This is the clinical picture most frequently seen. If treatment is begun at this time, complete recovery may be anticipated. In the absence of therapy, scar tissue forms, and after variable period of months or years, results in a complete fibrous ring.

2. *Rectal Stricture:* In our clinic this lesion is confined almost exclusively to Negro women. This is the experience of others (59), but the lesion is occasionally encountered in males (113).

The patient often complains of low grade constipation. Symptoms of tenesmus and pain are not conspicuous until the stricture is formed. On palpation an annular band is felt above the orifice narrowing the rectal lumen. Occasionally, obstruction is complete, necessitating colostomy. This is usually associated with edema resulting from extensive infection of the bowel wall. Rectovaginal fistula may occur spontaneously or following attempt at surgical repair. Of the 90 women seen by D'Aunoy and von Haam (59), 14 per cent had this complication.

3. *Lymphorrroids:* Following the formation of rectal stricture the lymphatic drainage of the lower rectum may be impaired. The result is similar to faulty venous return from this region when hemorrhoids form. In this instance anal tags appear which grossly are similar to hemorrhoids. Microscopically, these consist of dilated lymphatics, often thrombosed, with lymphocytes, eosinophils, monocytes and polymorphonuclear leukocytes diffusely scattered about the vessels. Lichtenstein (215) refers to these structures as "lymphorrroids." These tumors are indistinguishable from malignant neoplasms grossly and histopathologic study is necessary to rule out more harmful growths (333), (356). We have observed two patients, both colored; one male, the other female, with these anal masses. Both had been subjected to two "hemorrhoidectomies." On examination the tissue from both these patients were similar to those described by Lichtenstein.

G. Ocular Involvement. Levaditi and his co-workers in 1935 (208) inoculated the conjunctival sac of a chimpanzee with the virus of lymphogranuloma venereum and produced a purulent infection. The following year (200) they described a 37 year old man who had suffered for the previous six months with

follicular conjunctivitis and enlarged maxillary and post-auricular nodes. The patient had a positive Frei test, and material obtained from draining node caused meningo-encephalitis on injection in a monkey. An emulsion of the monkey's brain was inoculated into mice, which in turn developed the characteristic picture. A similar case was reported by Bollack, Basch and Desvignes (20). The virus was recovered from the enlarged preauricular lymph nodes.

Additional cases are reported by Ichijo (171) and by Hashimoto and his group (148), in which sterile antigen made from the ocular secretions gave positive cutaneous reactions in known lymphogranulomatous patients.

Carefully studied cases with recovery of the virus are reported in this country. Curth, Curth and Sanders (57) observed a patient with oculoglandular syndrome whose right eye had been inflamed for five years. A portion of the conjunctiva was excised and inoculated intracerebrally in a monkey with subsequent recovery of the agent. Acute eye infection in a laboratory worker is described by Oliphant, Powell and Perrin (259). The patient developed a positive Frei reaction and complement fixation test, and subsequently the virus was isolated by intracerebral inoculation in mice brain.

H. Meningitis. The virus was first isolated from the spinal fluid in 1936 by von Haam and D'Aunoy (141). They refer to ten patients who complained of severe frontal headaches, associated with signs of meningeal involvement. All had positive Frei tests, and lymph nodes on biopsy showed a histopathologic picture consistent with the diagnosis of lymphogranuloma. Pus aspirated from inguinal buboes caused a characteristic infection on intracerebral inoculation in mice in 9 of the 10 cases, and in two instances, spinal fluid was similarly infectious. In these two patients, there is clear evidence that the central nervous system had been involved.

Rajam (281) reported a patient with signs of meningeal irritation whose spinal fluid contained 135 cells with 90 per cent polymorphonuclear leukocytes, elevated gold curve, and sterile fluid which was antigenic when inoculated into a known Frei reactor. The patient developed high fever, convulsions, unconsciousness, and died. No autopsy was performed.

In 1942, Sabin and Aring (309) completely studied a patient who developed meningitis following a genital sore and bilateral inguinal adenopathy. The spinal fluid contained 4000 cells with 25 per cent polymorphonuclear leukocytes and 75 per cent lymphocytes. Protein varied from 250 mgm. to 1400 mgm. per cent. Sugar dropped from normal values to 17 mgm. per cent. The cerebrospinal fluid globulin was elevated as shown by a mastic curve of 5555432000. The virus was isolated from the spinal fluid, genital lesion, and buboes. Serum complement-fixation test was positive in dilution of 1/120, and there was cross agglutination with the agent of meningopneumonitis in dilution to 1/32.

Unproved Lesions

There are numerous pathologic lesions (Table 1) ascribed to the virus of lymphogranuloma venereum. The evidence on which this is based includes: clinical data, a positive Frei response, and, in some instances, inverted Frei test

(see page 38). However, since the virus has not actually been isolated from these lesions and transmitted to experimental animals, these cases are considered as unverified.

I. Ulcerative Colitis. Goodman (109) observed the co-existence of proctitis and ulcerative colitis in patients without rectal stricture who gave a positive Frei response. Because of this finding he emphasized the necessity for considering lymphogranuloma venereum in the differential diagnosis of chronic non-specific ulcerative colitis.

Because this syndrome is of unknown etiology and variable clinical and pathologic picture, Paulson (261) suggested that the virus of lymphogranuloma venereum may be the causative agent in some cases. He found that material prepared from the bowel contents of Frei-positive patients with colitis produced a positive skin test comparable to those induced by viral antigens (263). Control antigens of other viruses, and exudates of normal and diseased bowels and intestinal flora failed to elicit a similar response (267). Although this worker has not actually isolated the causative agent, this study strongly suggests the presence of the virus in the intestinal exudate (264), (265).

Palmer and his colleagues (260) have studied chronic inflammatory disease involving both colon and lower bowel in 76 patients. Lymphogranuloma was suspected in 10. From biopsy specimens of rectal mucosa, these workers isolated the virus in five instances by intracerebral inoculation into mice. However, they were unable to recover the organism from colonic ulcers or strictures from these same patients.

In 1941, Paulson (266) outlined a diagnostic routine for studying patients with ulcerative colitis in whom no apparent etiology can be found. He suggests that:

1. A Frei test be done and if positive,
2. Bowel antigens be collected and prepared as described by the author (262) and used for intracutaneous testing in the patient. This material is injected simultaneously with Frei antigen as a control. If positive, this "inverted Frei" test is highly suggestive.
3. Microscopic examination of rectal or colonic tissue should be performed.
4. Neutralizing test with the patient's serum should be carried out (page 39).
5. Animal inoculations of bowel antigen into mice or monkeys be performed and these brains be used as antigens for inoculation into known Frei-reacting patients.

J. Upper Intestinal Tract Infections. Coutts (44), (43) has written extensively about this problem. He contends that oral infection is not uncommon following cunnilingus. Recently, he has described micro-chaneres of the lips and tongue with concurrent pharyngitis and glossitis (50). Tonsillar infection with subsequent cervical adenitis has been ascribed to invasion by the virus (294).

Involvement of the right tonsillar fossa, pillars, soft palate, pharynx and larynx has been recorded in a 31 year old Negress by Myerson (252). The process consisted of a diffuse, irregularly distributed superficial ulcerated granulomatous lesion, covered by purulent exudate. An etiologic diagnosis was made be-

cause of a positive skin reaction, increased serum globulin, microscopic pathologic studies, and finally therapeutic response to intravenous Frei antigen.

Descending infection of the intestinal tract may occur and cases of linitis plastica, transient duodenal ulcers, and regional enteritis are described (50). The diagnosis in these cases was based on the roentgenographic and histopathologic picture, or on the finding of micro-corpuscles in the cells. The etiologic agent was apparently not recovered. Many attempts to isolate the causative agent from lesions of terminal ileitis have failed. The Frei intracutaneous test has been uniformly negative in patients with this syndrome according to Koster, Kasman and Scheinfeld (190), and Stafford (338). These studies have recently been extended by Rodaniche, Kirsner and Palmer (303), who observed four patients with regional enteritis and found that the skin was unresponsive to the antigen of lymphogranuloma venereum. These workers were unable to detect neutralizing antibodies in the sera of these patients, nor could they recover the virus from either the resected intestinal segments or from adjacent mesenteric lymph nodes.

K. Chronic Salpingitis and Parametritis. In 1938, D'Aunoy and Schenken (60) reported that lumbar pain is a frequent complaint in patients who also experience low abdominal distress suggesting salpingitis. In one instance, pelvic examination revealed a mass in the right lower quadrant. When this was excised and studied microscopically it was found to be studded with stellate abscesses surrounded by epithelioid and plasma cells.

A woman with symptoms of acute pelvic inflammation was explored by Franchi (88) who found a plastic process involving the adnexae. Purulent material removed from the site induced a positive response in known Frei reactors.

L. Skin and Subcutaneous Tissue. During the invasion period of lymphogranuloma venereum there are often dermatologic reactions of variable degree. Koppel (186) observed several cases of erythema nodosum and concurrent episcleritis. A similar case has recently been seen in this country (15). Hellerström found some dermal manifestation in 10 per cent of his patients, observing that it usually appears during the second month following the appearance of the buboes. Stannus (339) has noted that this skin response is more common following interference with the inguinal nodes, such as irradiation. Although erythema multiforme and erythema exudativum are less common, they have been described (98), (180). A scarlatiniform exanthem and also urticarial lesions have been described by Löhe and Blummers (216) and by Hoffman (163), in patients who have clinical evidence of this disease.

Melzer (231) has described bullous lesions on the abdomen. Material obtained from these lesions was infectious for guinea pigs.

Ulcerative skin lesions have been recorded by Chevallier and Bernard (37). These localized areas of cutaneous necrosis have been further classified by Wien and Perlstein (365), depending on whether the lesions are: (a) isolated dermal reactions, (b) secondary to lymph node fistulae formation, and (c) tissue destruction superimposed on esthiomène.

Gutman (136) believes that a diffuse erythema is the most common skin mani-

festation. This is due to local tissue hypersensitivity, the specific agent being of secondary importance. He, too, has noted erythema nodosum resulting in the course of severe reactions to Frei testing.

Sonek (334) has observed photosensitivity in 140 cases of 400 studied. This is manifest one to two months after the onset of bubo formation and occurred in 60 per cent of the chronic and about 20 per cent of subacute cases. Punctiform red papules appear on the skin one-half to three hours after exposure to sunlight. The author interprets this as an allergic phenomenon, and reports that accompanying this manifestation there was conjunctivitis in 19 per cent of the patients, joint involvement in 33 per cent, erythema nodosum in 16 per cent.

Sonek (337) further noted that this curious dermatologic characteristic occurred more commonly in women; in 42 per cent of one group studied. He believes it is associated with change in the serum proteins or lipoids.

Costello and De Oreo (42) reported an unusual example of skin and lymphatic involvement. A Negro seaman experienced swelling in the buttock one year after inguinal bubo inflammation. Multiple sinuses formed from the mass in the buttock, and purulent discharge was copious. The patient had a positive Frei test and microscopic study of the diseased tissue was compatible with a diagnosis of lymphogranuloma venereum.

Midana (236) noted multiple swellings and fistulae appearing over a period of years in the buttocks of a patient. Lipiodol injections outlined intercommunications of the fistulae and one was seen to pass through the sacrum and sacrococcygeal joint. It was presumed that the process arose from an area of proctitis, and had extended by contiguity along paths of least resistance.

M. Joint Involvement. Koppel (186) in 1927 described arthritis in three patients one of whom had polyarthritis together with erythema nodosum. Gutman (136) and Kornblith (188) have noted the presence of joint pains. We have observed this manifestation during the first weeks of the disease and have been impressed by the rapidity with which it responds to therapy. Counts (44) has published instances of acute arthritis simulating acute gonococcus invasion. In three cases there was effusion present and in one, the fluid was antigenic. Ruge has seen urticaria associated with arthralgia (308). Dawson says that he has seen arthritis in 16 patients (63).

Osteomyelitis of the mandible has been described by Slaughter (331). This occurred in a colored woman who entered the hospital in semi-coma with cervical adenitis and spinal fluid evidence of meningo-encephalitis. Pus removed from the bone induced a positive skin test in patients who were known Frei reactors. A case of complete destruction of the hip joint has been seen by Herzberg (160) in a soldier who developed arthritic pain one and a half years after inguinal involvement. Pus removed from the operative site induced a positive skin reaction. Another case of hip joint involvement two months after the appearance of buboes is described in a man of 35 (162). X-ray studies revealed decalcification of the joint, and following therapy there was restoration of the bony structure to normal.

A case of severe infection with complete necrosis of the hip with spread to

adjacent tissue, severe toxemia and death has been observed by Reichle and Conner (296). This patient was examined at necropsy and evidence of diffuse lymphocytic infiltration of many organs was found.

N. Lesions of the Head, Neck and Axilla. Fournier (87) believed that elephantiasis of the lips is often due to syphilis and he referred to this syndrome as "diffuse hypertrophic syphiloma." More recently, Netherton and Curtis (255) have described elephantiasis of the lips and of the genitalia occurring simultaneously in male patients with positive Frei tests, presumably both due to the virus of lymphogranuloma venereum. Ulcers of the tongue with enlarged submental, submaxillary and supraclavicular nodes are reported. The patient treated by David and Loring (61) experienced necrosis of the lymph nodes, and pus obtained gave a positive inverted Frei response. Curth (54) describes a patient who ten days previous practiced cunnilingus with a prostitute and de-



FIG. 4. AXILLARY ADENITIS

The aspirated pus induced a Feri reaction in a known lymphogranulomatous patient

veloped a herpetiform tongue lesion. This ulcerated and a bubo formed in the cervical region. Pus from the node was antigenic. Cunnilingus is said to be frequently responsible for mouth lesions (41), (28). Infection in the parotid region with fistulous tract formation is reported (41). Bloom (19) noted an ulcer with induration of the anterior one third of the tongue, and acute constitutional reaction. Destruction of the cervical nodes followed and when the discharge from these was injected into patients with lymphogranuloma a positive cutaneous test resulted. Biopsy of the buboes was consistent with the diagnosis.

The first instance of axillary infection is described by Klotz (182). He developed axillary adenitis following an initial finger lesion acquired by inoculating himself at the operating table while removing "hard inguinal buboes." The skin broke down with the appearance of multiple draining sinuses. A similar case of axillary involvement is shown in Fig. 4. Extragenital lesions of this sort are reported (147) in laboratory workers in close contact with the virus.

O. Urologic Lesions. Rodriguez Diaz (304) has described lymphangitis of the penis with extension to the lymphatics of the abdomen following intraurethral ulcers. The first case of recto-vesical fistula is described in a man who previously suffered from prostatitis. At operation peri-rectal inflammation was found with a tract running from the sigmoid to the bladder, entering the latter behind the trigone. A colostomy was done, and the fistula disappeared.

Rodriguez Diaz (304) has observed ulcerative lesions near the meatus in men with clinical evidence of lymphogranuloma but without recovery of the virus. When these heal they produce plaques with diminution in the calibre of the urethra resulting in dysuria. Vegetations formed with subsequent acute urinary retention. Endoscopic studies in these cases revealed edema of the vesical neck with extension to the bladder. The author describes increased vascularity with multiple polyposis simulating malignant neoplasms. In these cases the bladder may undergo localized necrosis requiring plastic repair. Usually such surgical procedures are unsatisfactory because of the friability of the tissues.

Coutts (47) has likewise seen edema of the meatus with engorgement of dorsal lymphatics of the penis. In these cases there may be urethral involvement as described below, with subsequent stricture. According to Coutts, the virus invades the submucosa and peri-urethral tissues and may eventually produce deformities of the vesical neck.

May (228) has observed similar lesions and also believes the virus of lymphogranuloma venereum is responsible for nodular peri-urethritis, verumontanitis, and epididymitis. This same author suggests that some cases of chronic balanitis with plastic induration of the penis may be caused by this agent.

In males, acute urethritis may follow within 4 to 17 days after sexual exposure. This syndrome is called "Waelsh urethritis." The discharge is less purulent than in gonococcal urethritis. Bizzozero and Midana (18) used this material as an antigen and obtained a positive test in known Frei reactors.

In the female, bladder lesions were described in 80 per cent of the cases of cervicitis. Endoscopic studies showed increased vascularization, congestion of the mucosa, and in some cases edema of the trigone reaching to the ureteral orifices. Rodriguez Diaz (304) observed destructive bladder lesions with esthiomène. In these cases the posterior portion of the bladder is involved.

Recently, Marshall and Endicott (224) reported a group of nine patients, seven women and two men, with "cystitis" of indeterminate origin. The cystoscopic picture varied in these patients, but all had positive Frei reactions or positive complement fixation tests, or both.

Perforations from urethra or bladder to vagina occur spontaneously and also following surgical intervention. This syndrome should always suggest lymphogranuloma venereum.

Additional Manifestations

P. Hyperpyrexia. Kornblith (188) has described cases of prolonged unexplained fever ultimately diagnosed as lymphogranuloma venereum. In the two patients discussed, there was a septic course with the temperature reaching 101 F. prior to bubo formation. Frei tests were positive. We have recently

seen similar cases. There may be hepatosplenomegaly associated with the syndrome (187), and also generalized lymphadenopathy.

Q. Pulmonary Infection. Experimental and pathologic studies suggest that hitherto unexplained syndromes may be initiated by the virus of lymphogranuloma venereum. The isolation of the virus from the lungs of patients with pneumonitis, or the "primary atypical pneumonias" has not been reported. The agent has been isolated from buboes of a patient with atypical pneumonitis by Martin and Wood (225), but final proof that the pulmonary symptoms are referable to this agent is not complete. Recovery in human cases of the closely related virus of psittacosis is described by Enders (72) and also by Meyers (233); and the isolation of a psittacosis-like virus from two fatal cases of atypical pneumonia by Eaton and his associates (68) makes it likely that, in some instances of pneumonitis, the agent of lymphogranuloma may be responsible (83).

The susceptibility of animal lung tissue has already been demonstrated (142), (326), and, although the portal of entry in a group of laboratory workers showing clinical evidence of infection is not known, it is likely that in two cases invasion occurred via the respiratory tract (147).

R. Ocular Lesions, Other than Conjunctivitis. In addition to the proved cases of the oculoglandular syndrome induced by the virus of lymphogranuloma venereum, several ocular lesions have been described which are attributed to viral invasion. Suspected but not proved cases of uveitis, conjunctivitis, and keratoconjunctivitis are described (15), (165). More recently, Macnie (220) has recorded several instances in which this etiology was suspected because of a positive Frei reaction. The author studied the effects of inoculation of the agent in the eyes of guinea pigs. Microscopic studies revealed the presence of polymorphonuclear leukocytes and monocytes in the conjunctiva, iris, and ciliary bodies. Santani and Sano (313) induced iritis, keratitis and conjunctivitis in rabbits by introducing virulent material, and subsequently recovered the virus.

Kitagawa (179) described fundal changes including peripapillary edema and tortuosity of the vessels in a series of 30 cases. Coutts (44) confirmed these findings.

S. Malignant Degeneration. Chronic irritation frequently precedes tumor formation. Reports of epidermoid carcinoma in patients with esthiomène are of particular interest in this connection. Because of the gross similarity in the appearance of these two ulcerative processes, the onset of the neoplastic degeneration may well be overlooked. Greenblatt (130) has called attention to the frequency with which genital malignancy may be confused with venereal diseases. He cites examples of tumor proliferation as a sequelae to venereal infection, and also malignancies mistaken for venereal disease. Deibert and Greenblatt (64) describe carcinoma arising in a patient of 24 years with elephantiasis of the vulva. The authors suggest that the lymphogranuloma may have supplied the stimulus for anaplasia. Study of 300 cases of rectal stricture by David and Loring (62) has revealed the formation of epidermoid carcinoma in four of them. Liccione (214) reported adenocarcinoma superimposed on rectal stricture in two Negresses. Greenblatt (130) after noting the development of cancer in a lymphogranulo-

matous lesion, suggests that chronic irritation is conducive to neoplastic change. Guzman (138) treated 12,546 patients with cancer at the Institute of Radium of Santiago. Of this number but nine had lymphogranuloma, and in eight of these cases the lesions were located in the rectum, genitalia or mouth; and histopathologic evidence suggested the simultaneous existence of both diseases in the same area.

Whether the chronic inflammation is responsible for the tumor proliferation, or whether the co-existence of the two processes in the cases described above, is coincidental, is a question. However, the role of biopsy cannot be over emphasized, and is indicated whenever genital or anorectal lesions fail to respond to therapy. This axiom has proved its worth according to Pund, Greenblatt and Huie (279), (130), and Pund and Greenblatt (278).

T. Influence on Reproduction. It is the impression of Wilson and Hesselstine (367) that lymphogranuloma does not induce sterility unless the disease involves the tubo-ovarian apparatus. In the cases studied they failed to notice any modification on the course of pregnancy, labor, or the appearance of the fetus in patients with latent infection.

In an experimental study, Hellendall (151) found that when pregnant mice are inoculated intracerebrally with the organisms of lymphogranuloma venereum, the virus may be recovered from the brains of the fetuses.

Grace (111) examined the semen of eleven men with asymptomatic lymphogranuloma venereum. The presence of the virus was sought by preparing the material as a Frei antigen and injecting 0.1 cc. intradermally into lymphogranulomatous patients. In no case was a positive reaction obtained and it was concluded that the virus is not present in detectable quantities.

U. Association with Other Diseases. Assuming that the Frei reaction is diagnostic of this infection in the absence of apparent lesion, double or multiple infections are not uncommon. About 40 per cent of the Negro patients in the Syphilis clinic of this Hospital give a positive response to the skin test. Robinson (298) and Bacon (2) and Shaffer and his associates (328) also report concurrent infections. Three patients in whom darkfield studies revealed *Treponema pallidum* in the genital lesions, and who subsequently developed inguinal adenopathy and positive Frei responses, are described by Sezary and Lenegre (321).

Coutts (46) has observed that the urethra of the male may be concurrently infected by the agents of gonorrhea and lymphogranuloma venereum. Under such circumstances, the incubation period for the latter is shortened and the infectious process accelerated. The edema of the meatus, the lymphaginitis of the coronal sulcus and dorsum of the penis usually appear a few days after the onset of urethral discharge.

Gaté and associates (102) have observed an instance where chancroid and lymphogranuloma venereum were acquired simultaneously. The genital lesions were characteristic of chancroid, but the patient developed a positive Frei test in addition to a positive Ducrey skin test. Subsequently the patient's wife developed enlarged buboes and skin sensitivity showing evidence of both venereal infections.

Engleson (73) described the appearance of genital lesions and buboes of lymphogranuloma in a patient with a positive Ducrey skin reaction. The nodes broke down and purulent material obtained gave a typical Frei reaction.

Ramel (288) isolated tubercle bacilli from a patient with genital lesion and lymphadenopathy characteristic of lymphogranuloma. The patient was later Frei test positive.

V. Childhood Infections. Infection in young children is not common, but when it occurs it is usually acquired through non-venereal contact. Lugan and Rotter (218) report finding glandular masses in the groins of three sisters, ages 6, 7, 15. These children had associated with their female cousin, who was believed to have acquired the disease from an infected sexual partner. Although the children's mother gave no history of similar illness, she and two cousins all showed positive Frei reactions. A case of inguinal adenopathy in a very young girl is described by Chevallier (38). The child gave a positive intradermal response to the antigen of lymphogranuloma. From this same clinic, a case of infection in a young boy is reported (34). Sonck (335) described rectal involvement in three sisters, all of whom were believed to be infected by their mother. This same author (336) recently recorded the sixth case seen in Finland in a girl of six with hemorrhagic proctitis and stricture. A girl of nine with enlarged inguinal buboes and positive Frei test came to the attention of Levy (212). She had previously had a negative skin reaction, but developed skin sensitivity under observation. Cases of proctitis due to lymphogranuloma in children have been described by Elitzak and Kornblith (71) and Bacon and Meharg (5).

These incidents of lymphogranuloma appear sufficiently frequently to justify investigating this disease as a possible entity in children with proctitis, inguinal adenopathy or such other syndromes as "idiopathic encephalitis."

W. Immunity. A single attack by the agent of lymphogranuloma venereum probably confers an effective and lasting immunity. This is in conformity with our knowledge of most virus infections as smallpox, chicken-pox, measles, mumps, cattle plague, swine fever, and dog distemper. In all these, one illness affords protection that, in the great majority of cases, extends throughout the life of the host (353).

The antibodies in sera are confined to the globulin component. During the course of the acute infection of lymphogranuloma, there is a conspicuous rise in the globulin fraction of the serum and Gutman and his associates (137) have determined that this elevation depends on increased euglobulin and pseudoglobulin. Immunity in general is linked with these protein fractions.

The complement-fixation test remains positive for 8-14 weeks in new-borns whose mothers have latent infections according to Levine, Bullowa and Scheinblum (210).

X. Lymphogranuloma as a Cause of Death. Rajam (281) observed a 27 year old patient with suppurating buboes and fever, terminating rapidly in convulsions, coma and death. The spinal fluid showed evidence of meningeal irritation and excited an allergic response in the skin of known Frei reactors. The virus was not isolated and an autopsy was not done, but it was the impression of the author

that the patient had died from an overwhelming infection by the virus. Reichle and Connor (296) studied a patient with infection of the hip joint, who subsequently developed peritonitis and died. At autopsy, the renal cortex showed numerous small, circumscribed areas of necrosis with focal collections of both lymphocytes and plasma cells. A similar type of kidney involvement is mentioned by Gutman (136), who also noted focal aggregates of round cells in the liver and spleen. At the Charity Hospital in New Orleans there were 11 deaths in two years in patients with rectal strictures (59). Two of these died of peritonitis caused by rupture of the stricture during dilation, and four others following colostomy. The remaining five patients died of debilitation and prostration attributed to the disease.

A remarkable case is cited by Pollard and Hellendall (273) of a thirty-two year old Negress who went into labor two weeks prior to term. Fetal respirations ceased, and four hours after parturition, the patient went into shock. At autopsy, granulomatous strictures of the sigmoid colon and rectum were found. Rupture of the latter was responsible for shock and death of the patient.

Since the introduction of chemo-therapeutic measures which largely eliminate radical surgical procedures, lymphogranuloma venereum as a cause of death will be seen with increasing rarity.

V. ETIOLOGY

A. *Isolation of Causative Agent*

Hellerström and Wassén (156) in 1930 announced the isolation of a virus from pus aseptically removed from an inguinal bubo. Monkeys inoculated intracerebrally developed the clinical and pathologic pictures of meningo-encephalitis. Cultures from the brains of these animals were bacteriologically sterile, and an extract of the meninges produced a positive skin test in a patient known to have lymphogranuloma venereum. The following year, Levaditi and his co-workers (199) repeated this experiment and maintained the virus for 12 passages intracerebrally in monkeys. This work has been amply confirmed and the causative agent has been obtained from the tissues of the primary genital lesions, pus of the inguinal buboes, the tissues of esthiomène, acute and chronically inflamed rectal mucosa, spinal fluid of patients with clinical evidence of meningitis, purulent discharge of patients with conjunctivitis, and from the cervix and urethra.

Prior to this work, various etiologic agents were suspected, including the organisms which cause syphilis, tuberculosis; and numerous cocci, bacilli, and protozoa. Retrospective analysis suggests that the confusion was caused by laboratory contamination or by mixed infections.

B. *Morphology*

Gamna (101) in 1924 described bell-like and horseshoe shaped structures in the cytoplasm of monocytes in cases of lymphogranuloma venereum. These, he believed, represented regression of the nuclear material. Miyagawa and his associates (210) reported the presence of irregular bodies in smear preparations

from both animal and human material which they believed were different from the bodies previously described by Gamna. These granulo-corpuscles may be detected by the Giemsa or Hosokawa stains. They are (241) found in monocytes, and less often in polymorphonuclear leukocytes and glial cells. They are often spherical, measuring between $0.2\ \mu$ and $0.3\ \mu$ in diameter. The arrangement is not uniform; they may be in pair or chain formation. The authors suggest that these bodies multiply and cause rupture of the cells. The cells with these elementary bodies contain large vacuoles within the cytoplasm, and the nucleus undergoes degeneration. This work was verified by Santani and Sano (313). Recently, Findlay and his associates (81) (82) have further elaborated this possible developmental cycle. Small elementary bodies measuring 100–200 millimicra were found in the cells of infected mice brain, and the authors report "these almost certainly represent the etiological agent of the disease" (305). These forms take a reddish-violet color with Giemsa and a blue color with Castaneda's stain. They have three distributions: (a) within the cell cytoplasm delimiting membrane, (b) diffusely scattered outside the cells in colony masses, (c) closely adherent to ruptured cells.

In addition, a larger type granule is seen after the period of rupture. These are three to four times the size of the elementary bodies. It is postulated that the smaller particles swell to become the larger ones. These may be further differentiated by staining characteristics. The larger particles divide until a compact mass forms from which smaller particles break off, and enter fresh cells.

A similar cycle is described in the yolk sac of the chicken embryo by Rake and Jones (283). They found that for the first ten to twelve hours, no bodies are discernible except those of the original inoculum. After this "silent period" the first particles seen are twice as large as the originally introduced elementary bodies. These continue to grow, up to $4\ \mu$ and occupy small vesicles in which they are imbedded. Vacuolated plaques, about $7\ \mu$ in diameter form, containing the elementary bodies. When these plaques disintegrate, the small elementary bodies are liberated, thus completing the first phase of the cycle.

There is again a "silent period" while the only particles present are the recently freed elementary bodies. Then after a period of ten to twelve hours these viral agents either re-enter fresh cells and repeat the process of the first phase of the cycle, or new vesicles form in which the elementary bodies multiply until they occupy the whole cell. Just prior to the death of the embryo, almost all cells are invaded.

Both groups of workers stressed the resemblance of this virus and the etiologic agent of psittacosis in morphology, developmental forms and staining characteristics.

C. Size

The virus can easily pass through such filters as Chamberland L2, L3, Berkefeld V and N and Seitz E.K. (242). The virus passes through collodion membranes with pores larger than $0.33\ \mu$ but it is retained by a membrane with pores smaller than $0.24\ \mu$. Miyagawa and his associates (242) found that the portion of

stock filtrate retained by the membrane with pore size of $0.24\ \mu$ or less is highly infectious, while the filtrates passing through the membrane had no power to produce typical lesions in mice.

D. Physical-Chemical Properties

1. *Resistance to Heat:* The virus remains virulent for 48 hours at $20^{\circ}\text{C}.$, but only for 24 hours at $30^{\circ}\text{C}.$ At $46^{\circ}\text{C}.$ it is no longer infectious after 20 minutes (244).

2. *Resistance to Cold:* Infected monkey brain retains its ability to produce symptoms for 22 days at $-5^{\circ}\text{C}.$ At $0^{\circ}\text{C}.$ it is virulent for 32 days (361). If infected mouse brain is frozen first and then dried in vacuum over sulfuric acid, virulence is retained for three months (78). The virus is now maintained for years without loss of virulence at $-72^{\circ}\text{C}.$ after dehydration (85).

3. *Resistance to Desiccation:* Levaditi (196) found the power of infection diminishes when virulent monkey brain is dried in vacuum over sulfuric acid at $20^{\circ}\text{C}.$, so that after eight or ten days, it no longer causes meningo-encephalitis in mice. However, if it is first frozen and then dried in vacuum over sulfuric acid, virulence is retained for three months (78).

4. *Resistance to Antiseptics:* Formalin 1-1000 arrests the virus activity while hydrogen dioxide and Lugol's solution do not. D'Aunoy and von Haam (59) found that acriflavine 1-100,000 inactivates the virus but only in the presence of light.

5. *Maintenance in Glycerine:* Hellström and Wassén (157) found in 1930, in their original study on the isolation of the agent, that it may be retained in glycerine without loss of virulence for only seven days at $5^{\circ}\text{C}.$ This is in contrast with the agents of smallpox, vaccinia, herpes, poliomyelitis and rabies which display considerable resistance in glycerine for months.

6. *Polarity of the Virus:* When the virus is put into an electrophoresis apparatus and current is allowed to act on the bath, it is found that the fluid at the positive pole contains the infectious material. Intracerebral inoculation of this material induces the typical meningeal changes. The organisms of herpes and encephalitis likewise concentrate at the positive pole (195), (196).

E. Studies in Experimental Animals

1. *Histologic Reaction:* The mouse was first used in experimental studies in 1932, and is the most convenient laboratory animal for this work. According to Findlay (77), the essential histopathologic changes consist of proliferation of endothelial cells lining the lymph channels. In the brain, this cellular reaction occurs in the Virchow-Robbins space and extends along the vessels as they penetrate the subarachnoid space. In addition to this perivascular cuffing, clusters of cells are found in the parenchyma subjacent to the pia-arachnoid. These cells include polymorphonuclear leukocytes, large and small lymphocytes and plasma cells.

2. *Receptive Animals:* Hellström and Wassén (157) testify that *Macacus rhesus* is less receptive than *Macacus cynomolgus* or *Macacus inuis*. Von Haam

(139) has succeeded in maintaining one strain of virus for three years by bi-weekly transfers through mouse brain, and Grace (115) has carried one strain for six years by weekly transfers. Findlay (77) found that after intracerebral inoculations into rabbits and field moles, the virus is harbored without producing pathologic changes. Dogs are receptive to the virus. Levaditi and his group (207) found that the cat responds to brain inoculation. Miyagawa and his associates (246) report that the albino rat and domestic fowl fail to show changes after brain injections. Reports on the guinea pig vary (122). Findlay (77) could not infect the rat, but Wassén (360) was successful. According to D'Aunoy and von Haam, ferrets are receptive, but sheep, squirrels, calves and frogs, less so (59).

3. *Routes of Inoculation:* (a) *Intracerebral:* Numerous reports testify that this is the method of choice in most animals.

(b) *Cutaneous:* Hellström and Wassén (361) observed that following inoculation into the prepuce of the *Macacus rhesus*, the animal develops bilateral inguinal adenitis with typical pathologic changes. The same authors scarified the skin of a monkey and rubbed virulent tissues on this area. The adjacent lymph nodes became infected. Intracutaneous injections into guinea pigs, fowl, and squirrels result in the appearance of papules from which the virus may be recovered.

(c) *Intraperitoneal:* When the virus is injected by the intraperitoneal route into monkeys, the omentum and mesenteric nodes become infected. The mouse does not develop meningo-encephalitis following intraperitoneal inoculation, unless the brain is traumatized first (77).

(d) *Corneal Implantation:* Levaditi and his collaborators (208) induced keratitis in the chimpanzee by inoculating bubo pus from an infected patient into the cornea. This same technique has been used in the rabbit and guinea pig by Santani and Sano (313).

4. *Organs From Which the Virus has been Recovered:* Following intracerebral inoculation into mice the virus has been recovered from the brain, kidney, lymph nodes and blood, but not from liver or spleen. Following intraperitoneal inoculation, the organism is obtained from all the above organs and in addition from the liver and the spleen (205). Following intracerebral inoculation into monkeys (199) the virus may be isolated from the brain, liver, spleen, kidney, bone-marrow, and lymph nodes.

F. Cultivation of the Virus

1. *Chicken Embryo Studies:* In 1935, Miyagawa and his associates (243) reported that the virus could be grown on the chorioallantoic membrane of a ten-day chick embryo. A plaque formed from which the granulocorpuscles could be demonstrated. Reinoculation into mice caused typical meningo-encephalitis. Later Rake and his associates (283) observed that the yolk sac is a more favorable site. Howard and Hull (167) also found the yolk sac more satisfactory and noted that the lesion formed could not be distinguished macroscopically from that of

other virus infections, but microscopically the lesion bore resemblance to the stellate abscesses of human tissue.

2. *Tissue Culture Studies*: Miyagawa in 1936 (245) successfully transferred the organism to tissue fragments made up of spleen, testicle, and brain of the normal mouse. The virus was carried through two generations without loss of virulence. Nauck in 1937 (253) and Malamos (222) cultivated the agent in media from the rabbit cornea. Gey and Bang (106) studied cytopathologic changes in human fibroblasts maintained by the roller tube method. These authors described the development of typical granulocorpuscles. These infected cells produced meningo-encephalitis on reinoculation into mice. Growth was deterred when sulfanilamide was added. Sanders (311) found embryonic guinea pig brain and serum the most efficient vehicle for propagation of the virus.

G. Toxic Factor Associated with the Agent

In 1943, Rake and Jones (285) postulated the presence of a toxic factor produced by the virus of lymphogranuloma venereum. However, in so far as they were unable to dissociate the "toxin" from the viral particles, the existence of a "toxic factor" cannot as yet be accepted.

H. Virulence Studies

Grace and Suskind (119) noted increase in virulence with repeated passages through 35 generations of mice brain. However, there is a loss of virulence by repeated transfers intradermally into guinea pigs (122). When the agent is again introduced into mice after these passages through guinea pigs, there is no apparent loss of infectivity for the mouse. Levaditi and associates (197) obtained a strain of virus from a human lymph node and after 12 transfers intracerebrally in monkeys, found that reinoculation into the prepuce of man induced bubo formation in 35 days with the characteristic clinical picture of lymphogranuloma venereum. These same authors found that a virus which had demonstrated its virulence for monkey would fail to kill mice but on reinoculation of these emulsified mouse brains into monkeys, encephalitis was produced.

Sanders (311) noted that with repeated transfers in tissue culture, virulence was increased by keeping the cultures at 23°C. rather than 37°C. Rodaniche (301) showed that although there was an initial difference in virulence in five strains isolated from patients, after several passages in mouse brain all strains had essentially equal killing power.

I. Immunologic Studies

1. *Viral Antibodies*: Levaditi and his collaborators (206) observed that infected patients possess substances in their sera which will neutralize virulent lymphogranuloma virus. In 1931, they reported that when the infectious agents are first incubated with sera of patients with clinical manifestations of this disease and subsequently inoculated into monkeys, the animals will not develop symptoms.

The following year (202) they demonstrated that the mouse is a suitable animal for these studies, and outlined the following technique for demonstration of the protective bodies:

a. Human serum which has been stored at 5°C. is incubated with equal parts of infected mouse brain suspension for 90 minutes at 37°C., and then at 5°C. for 17 hours.

b. One drop of this mixture is then inoculated into mice intracerebrally.

c. The animals are sacrificed at 24 days.

d. If the patient's serum contains protective bodies, the mouse brain will show no meningo-encephalitis.

Findlay (76) made use of this procedure to show that climatic bubo and lymphogranuloma venereum are the same disease. He observed that the virus of the latter syndrome is neutralized by the sera of patients with climatic buboes. Wassén (361) determined that these neutralizing properties appear between the 12th and 17th day. The same author reported that injection of virulent material intracutaneously into guinea pigs will cause production of a papule in two to three days at the site of inoculation, but after incubation of the virulent material with convalescent sera, the papule does not appear. However, when the sera are first inactivated by heating for one hour at 60°C. the viral neutralizing properties are destroyed. Wassén (361) also found that these same substances which protect the mouse from meningo-encephalitis are sometimes found in control patients with no evidence of infection by the virus.

2. *Complement Fixation*: McKee and her associates (229) have shown that sera from infected patients contain a substance which will fix complement in the presence of the viral antigen. By varying the amount of serum used it is possible to find the "titre" at which the complement is fixed. The complement-fixation test has proved to be a valuable diagnostic aid (286), (327), (114).

J. Relationship to Other Pathogenic Agents

In recent years evidence has accumulated pointing to a relationship among several pathogenic viruses, namely, psittacosis, trachoma, inclusion blennorrhoea conjunctivitis, meningo-pneumonitis virus of Francis and Magill, and pneumonitis viruses isolated from cases of atypical pneumonia, and lymphogranuloma venereum.

Developmental forms of the psittacosis virus were first described by Bedson and Bland (10). Subsequent studies by these authors (11) revealed that an apparent cycle exists, in which the elementary bodies divide, the fragments expand into larger initial bodies, and these in turn give rise to the smaller elementary bodies. Rake and Jones (283) studied the developmental forms of lymphogranuloma and noted similarity in the morphologic characteristics of this agent and that of psittacosis.

Thygeson (350) followed the transformation of elementary bodies to larger plaques, with reappearance of elementary bodies in inclusion blennorrhoea, and also in trachoma (349) and added that the cytoplasm surrounding these viral

bodies contains glycogen, whereas none could be found about the agents of lymphogranuloma venereum or psittacosis (351), (352), (287).

In 1938, Francis and Magill (90) isolated an agent from the nasal washings of a patient with a respiratory infection. It produced meningitis and pneumonitis in mice and hence is referred to as the agent of meningo-pneumonitis. These authors have been unable to find complement-fixing antibodies for this agent in the original patient or any other human, and it is suggested by Magill (221) that it is possible this virus is not a human invader, but a contaminant in the passage animals used. The virus is about the same size as the one of lymphogranuloma, but the authors were never able to produce cross-immunity between these agents.

Eaton, Martin and Beck (69) describe an apparent antigenic relationship between the viruses of lymphogranuloma venereum and meningopneumonitis. In mice immunized by intracerebral or intranasal inoculation a reciprocal partial cross-immunity was demonstrated. Sera of animals immunized with these viruses showed cross-reaction by complement fixation with antigens of the viruses. Hamsters, white rats, and kangaroo rats that recovered from intracerebral infection with the virus of lymphogranuloma were more resistant than control animals to subsequent inoculation with the virus of meningopneumonitis. These workers were unable to demonstrate a similar cross-immunity between the agents of lymphogranuloma and psittacosis.

Beck and Eaton (9) isolated a viral agent from two nonfatal cases of atypical pneumonia which had previously been exposed to two fatal cases. The agents obtained from the two non-fatal cases were identical with each other as shown by cross-immunity experiments, and sera from these two patients fixed complement in the presence of antigens of mouse meningopneumonitis and psittacosis. Also mice actively immunized with the psittacosis virus were protected from the mouse meningopneumonitis virus. Further studies revealed that the virus from the cases of human atypical pneumonia when inoculated intracerebrally, protected mice from 1000 M.L.D. of psittacosis introduced intracerebrally.

Rake and his associates (282) studied cross reactions in complement fixation tests with the antigens of psittacosis, meningopneumonitis, lymphogranuloma venereum and the sera from cases of psittacosis, lymphogranuloma and atypical pneumonia. These investigations revealed that sera from patients with lymphogranuloma venereum fix their homologous antigen and those of psittacosis and meningopneumonitis; sera from cases of psittacosis bind complement in the presence of the antigens prepared from the homologous agent and that of lymphogranuloma; sera from certain cases with atypical pneumonia fix antigens of all three agents. None of the antigens gave fixation with normal human sera. Five of the eight patients with atypical pneumonitis, etiology unknown, reacted positively to intradermal injection with Frei antigen. Smadel and his collaborators (332) reported that the common antigen factor found in both members of the lymphogranuloma-psittacosis group was present in approximately equal amounts in both agents studied in their laboratory so that complement fixation tests were not satisfactory for distinguishing one virus from the other. Like-

wise, although slight differences were found in the antibody titers of certain sera when tested with the two antigens, these were neither sufficiently great nor consistent enough to enable the authors to differentiate human infections induced by the two viruses.

According to Rake and his group (284) 'the agents of trachoma, inclusion blenorrhea, lymphogranuloma venereum, and pneumonitis of mice are all susceptible to the chemotherapeutic action of the sulfonamides.

Sabin and Aring found (309) that serum from a patient with fulminating infection and meningitis due to the virus of lymphogranuloma fixed complement with the virus of meningo-pneumonitis, but not with the agents of lymphocytic choriomeningitis, St. Louis, Eastern or Western equine encephalitis.

From these investigations it is probable that some group antigenic relationship exists among the agents of lymphogranuloma venereum, psittacosis, inclusion blennorrhea conjunctivitis, mouse meningopneumonitis, and some agents capable of producing atypical pneumonia.

VI. PATHOLOGY AND PATHOGENESIS

We have examined biopsy specimens from the Surgical Pathology collection of the Johns Hopkins Hospital and the following descriptions are based on this material and data from the literature.

A. Primary Genital Lesions

These lesions have been described in detail by Stannus (339). The inflammatory reaction excited at the primary site may be a vesicle or chancre. Grossly, these lesions are not conspicuous, rarely attaining a size of one centimeter, and usually but several millimeters. Microscopically, there are no distinguishing characteristics. There is thickening of the stratum spinosum and the rete pegs and papillae are infiltrated with lymphocytes, some plasma cells and polymorphonuclear leukocytes. These inflammatory cells penetrate to the corium, and the subcutaneous vessels are not involved as in syphilis. At the points of ulceration, the polymorphonuclear leukocytes predominate.

Incubation Period: The interval from sexual exposure to the appearance of a genital lesion may vary within wide limits. Most experiences place this period at from 3 to 21 days (98), (153), (254). Sezary and Friedmann (319), who believed they could date this interim, noticed lesions as early as two days and as late as 30 days in eleven cases. Prehn (276) claims to have seen initial manifestations within one day, and as late as 67 days. When the virus is introduced experimentally into the foreskin of man, a vesicle appears in 7 to 21 days according to Wassén (361).

B. Buboës

These have been described in detail by Durand, Nicholas and Favre in 1913 (67). In this country D'Aunoy and von Haam (59) have substantiated the essential findings. The lymph nodes are adherent to each other and to the skin, due to a capsular inflammatory reaction which is one of the characteristic features of this process.

On section, the appearance of the cut surface varies according to the degree of vascularization. Color is at first greyish red, changing to deep red as the process advances. Yellowish pus exudes from localized areas on the cut surface. The nodes are moist and boggy. The parenchyma bulges above the capsule, suggesting increase in tension. Microscopically, there is proliferation of all the lymphoid elements. The essential lesion consists of minute irregular abscesses (Fig. 5), with a core of cellular and nuclear debris and polymorphonuclear leucocytes, surrounded by a peripheral zone of other cells, predominantly monocytes. In later stages, large mononuclear cells may be arranged in epi-

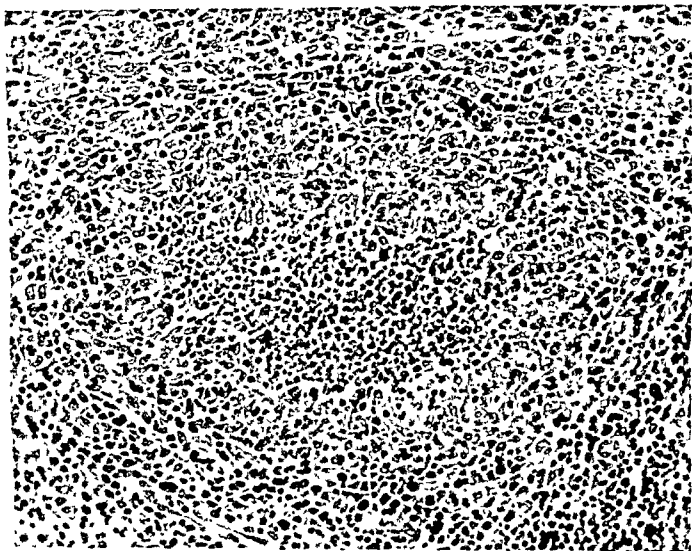


FIG. 5. Photomicrograph $\times 250$

Abscess in lymph node infected by the virus of lymphogranuloma venereum

thelioid formation. This organization has led some earlier workers to confuse this lesion with tuberculosis and syphilis. In areas between the abscesses, occasional clusters of eosinophils and multinucleated giant cells are often present.

Occasionally the minute abscesses coalesce, so that one sinus tract appears on the skin, as in chancroid. Usually, they penetrate through the capsule, subcutaneous tissues and skin, so that multiple draining sinuses appear on the surface. The capsular reaction is extensive, accounting for the plastic periadenitis.

Incubation Period: As with the genital lesions, this period varies. Inguinal adenopathy usually begins two weeks to three months after coitus (59), (364), (319), but limits from one day to six months are recorded (276). Occasionally the

lymph node enlargement is noticed before the genital lesion. Wassén (361) found that in experimentally infected patients, the regional nodes are palpable in 15 to 20 days after inoculation of the virus into the foreskin. It is stated that in naturally acquired disease the incubation period is shorter in warmer climates, and buboes have been observed within six days of venereal contact (254).

C. Probable Pathogenesis of Constitutional Reactions

The symptoms associated with the active infection may be explained by two factors:—the direct effect of the invading organism or its toxin; and the allergic response of the host. Evidence exists that both mechanisms operate to produce the constitutional reactions seen in this disease.

1 (a) *Invading organisms*: In 1936, von Haam and D'Aunoy (140) postulated that generalized dissemination of the virus is the factor responsible for the clinical syndrome that is commonly seen during the initial phases of the disease. They assumed that the virus is distributed throughout the host during the incipient stages of the infection. This hypothesis is based in part on the finding of the virus in various organs following intracerebral inoculations of monkeys (199). However, successful isolation of the agent from the peripheral blood has not been attained.

(b) *"Toxic" factor*: In 1939, Gutman (136) suggested the possibility of a "toxic" factor as the cause for the systemic manifestation of the infection, and acknowledged the difficulties in proving such a hypothesis. Recently, Rake and Jones (285) have reported isolating a "toxic" substance from infected yolk sac which has a lethal action on mice.

2. *Hypersensitivity*: The intracutaneous skin reaction of Frei (92) depends on a mechanism of hypersensitivity, that is, the body has an increased specific reaction capacity not found in the normal individual. It is generally believed that erythema nodosum which occurs with such frequency in this disease is an expression of hypersensitivity. Hellerström (152) offered this suggestion and it is substantiated by the frequent occurrence of this cutaneous manifestation following severe reaction during the Frei test (32). Arthritis may be such an allergic phenomenon.

D. Elephantiasis of the External Genitalia

This lesion is more common in the female than in the male. Ulceration of the overlying skin is common, and according to Kampmeier (177) such areas of epidermal destruction are invaded by polymorphonuclear leukocytes. The corium is edematous and infiltrated with both leukocytes and plasma cells. Thrombosis of small vessels occurs with infarction of the adjacent tissue. D'Aunoy and von Haam (59) say that the process consists of thrombo-endolymphangitis and perilymphangitis, with spread from the infected nodes to the surrounding tissues. If the infected genitalia remain untreated, fibroblasts appear, with subsequent sclerosing and hardening of the region involved.

In explanation of the vulvar elephantiasis, it has been suggested that involvement of the inguinal nodes blocks the lymphatics from the external genitalia.

A more plausible theory is that the inflammation within the genitalia results from direct action of the virus. It is difficult to induce chronic edema in an area by interfering with lymph drainage. Support to the concept of the local action of the virus is given by the work of Koch (184), who recovered the virus from biopsy material in cases of esthiomène. Levaditi and Simon (209) were unable to isolate the agent.

E. Rectal Involvement

The essential lesion of proctitis is ulceration of the rectal mucosa with penetration of the muscle layer by plasma cells, lymphocytes and some polymorpho-



FIG. 6. Photomicrograph $\times 50$
Acute proctitis due to lymphogranuloma venereum

nuclear leukocytes, with dilatation of the lymphatics and blood vessels (Fig. 6). After a period of months or even years, scar tissue is laid down and rectal stricture results. Much of the superficial portions of this ring of scar tissue is composed of edematous granulation tissue. Secondary infection is inevitable, and increases the rectal discharge. Hemorrhage follows erosion of the small vessels. Pain does not become conspicuous until the stricture is well formed.

The relationship of rectal lesions to sex has caused much debate. It has been assumed that bubo formation in the male is directly related to the fact that the lymphatics of the penis drain to the superficial inguinal nodes. However, in the female only the lymphatic channels in the labia majora communicate with the inguinal area, while those in the posterior portion of the vagina and cervix drain into the external iliac nodes (53). It has been suggested that this accounts for

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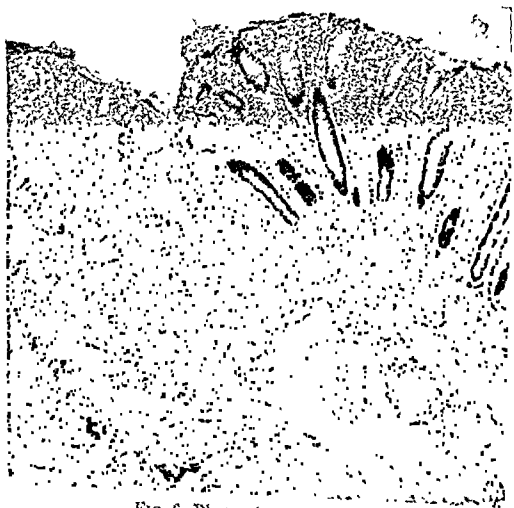


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the infrequency of inguinal involvement and the common rectal involvement in women. However, Bensaude and Lambling (16) believe that the virus migrates directly from the vagina to the perirectal wall, and that scarring presumably begins in the deeper layers of the rectum before the mucosa is affected. These authors offer as evidence the fact that, of 88 women with stricture, only 12 had active proctitis. On the other hand, Grace (113) has found that of 67 women with rectal stricture, 92 per cent had accompanying proctitis. He has suggested that the virus comes in contact with the rectal mucosa shortly after coitus because of the contiguity of the vulvar and anal mucosa.

Bensaude and Lambling found that in 78 of 80 male patients with rectal stricture, there was concurrent proctitis, and are of the opinion that this results from direct implantation of the virus on the mucosa during pederasty. Eighty per cent of their patients acknowledged this practice. Grace (116) also observed this association of rectal infection and homosexuality.

In our own experience, rectal involvement due to lymphogranuloma is infrequent except in colored women.

In 1935 Levaditi and his group (191), (247), (198) isolated the virus from a patient with inflamed rectal tissue, and then produced the characteristic histologic lesions in a chimpanzee by direct inoculation. Findlay (77) further clarified the problem by isolating the agent from the inguinal nodes of a patient and injecting this material into the rectal mucosa of a monkey. Subsequently the animal was sacrificed and the mucosa was found to be histologically indistinguishable from that of a naturally infected human case. From the tissue a virus was recovered which induced typical meningo-encephalitis in mice. Findlay concluded that "there is little doubt that the same virus is responsible for the genital lesions of lymphogranuloma venereum, and the rectal lesions associated with certain cases of stricture."

VII. DIAGNOSIS OF LYMPHOGRANULOMA VENEREUM

Although the clinical manifestations of lymphogranuloma venereum are varied, no one lesion is pathognomonic. There are numerous causes for genital or rectal lesions, for adenopathy, and for the other entities described in the previous section, so that differential diagnosis exclusively on clinical grounds is difficult. Several diagnostic laboratory procedures are available for routine use, and other supplementary aids may be utilized in special studies.

A. Skin Sensitivity Tests

Since 1925, the intradermal test introduced by Frei (91) has been the main approach to the diagnosis of this venereal disease. Although the original Frei test was performed with human pus, other antigens are now available.

1. *Human Pus Antigen:* According to the original description, pus is aspirated from an unruptured bubo of a patient infected with the virus of lymphogranuloma venereum. This is diluted with six volumes of salt solution and heated to 60°C. for two hours on one day, and to the same temperature for one hour on the following day. One-tenth cc. is injected intracutaneously, and, if a papule more

than 6-7 millimeters in diameter forms after 48 to 72 hours, this is indicative of current or previous infection. A dry pus antigen may be prepared without loss of potency according to Grace (110). Retention of potency of this preparation for as long as three years has been recorded (145).

Frei (100) asserts that the test is highly specific. The test may be falsely negative if the antigen is improperly prepared; e.g., when it is heated to 80°C. or higher. Suspected false positives require careful evaluation. It is essential that the papule be of the required size; erythema is of no significance. Frei (95) has found that the most common cause of error in the presence of false reactions is contamination of vaccines with living or dead bacteria which may result in inflammatory reaction. In studying the histology of specific and non-specific responses in patients known to have lymphogranuloma venereum, Franchi (89) found that the former have the appearance of tubercloid reactions, with monocytes and lymphocytes predominating, whereas the reactions induced with streptococci and staphylococci show only acute inflammation with polymorphonuclear leukocytes in abundance.

The main objections voiced against the human antigen are that infected patients may not always be available from whom to obtain the material, that one cannot be certain these patients do not have other infections, and that, because of variation in its preparation in different laboratories (286), results are not comparable.

2. Animal Tissue Antigens: After Hellerström and Wassén succeeded in producing infection in monkey brains, they studied this tissue as a source of antigen. Satisfactory results were observed, using the brains of 65 monkeys. Papules up to 8 millimeters in size were obtained. Brain tissue that showed no evidence of meningo-encephalitis gave negative results. Injection of extracts from the suppurating mesenteric glands of infected guinea-pigs produced comparable reactions (234). Wassén (360) was the first to investigate the use of extracts of virulent mouse-brain as a source of antigenic material. In all patients that gave a positive response to human bubo-pus, he obtained a powerful reaction, up to 20 millimeters, with mouse brain extracts. However, control patients showing no clinical or laboratory evidence of infection gave positive responses, up to 10 millimeters; and non-infected mice brain induced small papules in both diseased and non-infected patients. It was concluded that this product is not very suitable for testing purposes. Strauss and Howard (343) found that about half of the reactions were falsely positive in normal non-infected subjects, especially when material stored a month or more was used. Binkley and Love (17) reported false reactions in 45 per cent of their tested individuals. Grace and Suskind also cultivated the virus in mouse brain (120), and, in contrast to the unsatisfactory results generally reported, claimed that not one false positive reaction was seen in nonlymphogranulomatous persons, and that emulsions of normal mouse brain did not produce false response in either infected or non-infected people. They reported that quantitatively, the results were the same as those produced by human pus, but qualitatively, the reactions were usually more intense. No desensitization of the skin of infected subjects

was observed after repeated inoculations. Mouse brain antigen retains its potency for at least eight months (121). It is conceded that whenever this antigen is used it is essential that control material consisting of non-infected mouse brain be used simultaneously to eliminate non-specific false reactions induced by foreign animal protein.

3. *Yolk Sac Antigen*: Grace and his collaborators felt that a suspension of elementary bodies of the virus might be the ideal agent for the performance of the Frei test. The virus was grown on the yolk sac of developing chicken embryo (117) and then harvested. Formalin-saline and then phenol were added to maintain bacteriologic sterility. Control material was produced in exactly the same way from normal yolk sac from ten day embryos. These materials were tested on clinically lymphogranulomatous persons and subjects showing no evidence of infection. Twenty-two of 26 tested cases, known to have the disease, gave positive responses. In normal people, the infected yolk sac antigen produced papules but always less than 5 millimeters. These results were considered satisfactory. Parallel studies with yolk sac antigen revealed superiority over mouse brain antigen in both sensitivity and specificity. Sulkin (344) concurred in this opinion, finding the mouse tissue less satisfactory in 42 infected and 20 non-infected subjects. Greenblatt (131) analyzed results with human pus, mouse brain, and antigen of chick embryo origin, and found the yolk sac material the most satisfactory. Rake and his associates (286) attest to the superiority of the yolk sac antigen. Curth (56) conducted a study to evaluate the relative merits of human pus and antigen from the yolk sac of the chicken embryo. In 69 patients in whom the diagnosis was not in doubt, positive reactions were obtained with both antigenic materials. However, when 90 subjects, with neither history nor physical evidence of the infection were tested, none exhibited cutaneous hypersensitivity to human bubo pus, but 22 gave positive responses to egg yolk antigen. This worker concluded that the human material is superior.

In summary, it appears that the yolk sac material is more specific than mouse brain extract and as sensitive as human material. Its chief value lies in the fact that it may be prepared under standardized conditions, free from contamination, and that the virulence and dilution of the virus may be controlled. The test is performed and evaluated in a manner similar to that of the original Frei test.

4. *Time for Development of Sensitivity*: Because the exact day of infection is difficult to determine, one cannot fix with certainty the time required for the skin sensitivity to develop. However, Hellerström reported that 8 cases were Frei-positive 1 to 3 weeks after the appearance of the buboes, 14 cases after 4 weeks, 5 cases after 6 weeks, 2 cases after 8 weeks. Nicolau and Banciu (257) noted the presence of cutaneous allergy as early as the tenth day after the appearance of the primary lesion, but the full intensity of the reaction was not reached until the fourth to sixth week. Wilmoth (366) believes that the Frei test becomes positive fifteen days after the start of the infection, and is usually maximal after an additional week. Wassén (361) recorded his results in psychotic patients experimentally infected who were either inoculated into the prepuce with living virus or treated with the same agent following scarification of the skin. Four

patients inoculated directly into the prepuce responded to intradermal Frei antigen as early as the sixth day with papules 6 millimeters in diameter. Two subjects whose skin was scarified developed skin sensitivity by the thirteenth day. The papules resulting from the testing remained just as long as those associated with ordinary infections: namely, eight to twelve days. Although skin reactivity usually appears within three weeks, delay as long as three months is not uncommon (276).

5. *Duration of Skin Sensitivity:* In the experimental study described by Wassén, cutaneous response to human bubo pus remained as long as 290 to 398 days. In the naturally acquired disease, the Frei test may be active for as long as thirty years according to Hellerström (quoted by Wassén), and Palmer and his associates (260) have seen positive reactions as long as twenty-one years after infection. Once the test becomes positive, it probably remains so for the life of the patient (112), except in rare instances where immediate sulfonamide therapy has caused reversal (340). We have had the opportunity of observing reversal of cutaneous sensitivity in several instances.

6. *Interpretation of the Frei Test:* Connor and his associates (40) reported the results of studies of 1,265 patients; of these, 243 gave persistently positive reactions and all but 17, or 7 per cent, had a history typical of infection, or showed clinical manifestations. In spite of repeated testing of patients with negative reactions, no instance was observed in which allergy to the antigen was produced. D'Aunoy and von Haam (58) found, in testing 500 infected patients and 800 controls, that they obtained 98.1 per cent correct results.

In one study of 1,170 tests on 400 patients, accurate results were claimed in 95 per cent of the reactions (84). Bacon reviewed the findings from 41 clinics for the American Proctologic Society and learned that 35 reporting members obtained satisfactory results in over 90 per cent of their cases (2).

The specificity of the Frei test with any antigen is still questioned by Brandt and Torpin (27), Knott and his associates (183), and by Robinson (298). They suggest that cross reactions may occur in persons with other venereal diseases, especially syphilis and chancroid; and the high incidence of positive reactors among apparently normal Negroes suggests the possibility of false reaction in this race, perhaps due to some unknown peculiarity of the skin. This idea is refuted by others (94), (118). False positive reactions have been described in atypical pneumonia of unknown etiology (282).

However this may be, a positive Frei reaction does not identify any lesion as lymphogranulomatous unless the test, originally negative, has been observed to become positive on repetition at short intervals. Otherwise, a positive Frei test indicates only that the patient has at some time been infected with the virus; and it has no necessary bearing on the nature of the presenting lesion. On the other hand, a repeatedly negative Frei test in a patient suspected of having lymphogranuloma is reasonably strong evidence of the absence of this disease, except in those few cases which exhibit anergy (91).

7. *Non-responsiveness in Infected Patients:* Frei warns (95) that a negative result should not be taken as proof that the patient does not have lymphogranuloma

if the clinical evidence is controversial. He suggests (96) that under such circumstances an inverted or intravenous test may be of assistance. This failure to respond to the injection of the antigen is termed "anergy." Such a phenomenon is described (310) in a patient with typical genital lesion, buboes, and clinical course, who was non-responsive to 9 different potent antigens; but pus removed from the patient's bubo excited a clear-cut reaction in other infected patients. Temporary anergy, lasting for six months, is described by Prehn (276). After this interval the patient responded in usual fashion. In two of the patients experimentally infected by Wassén, skin sensitivity was lost in two cases after forty days, although previous reactions were of diagnostic significance (361).

B. Complement-Fixation

The complement fixing property of lymphogranulomatous antigen derived from human bubo pus was demonstrated by Melczer and Sipos (232). These investigators found virulent human antigen superior to extracts of mouse brain and nodes from guinea pigs and rabbits. The bubo extract gave positive fixation in 85 per cent of 22 infected patients, and 13.5 per cent false positive tests among 86 control patients with syphilis and gonorrhea. It is possible that some of the control group had latent infections with lymphogranuloma.

Midana (238) used a similar technique, but reported the procedure of little diagnostic value. A crude extract, made by mixing bubo pus and saline and then using the supernatant after centrifugation, successfully fixed complement in the presence of sera from infected patients, according to Coutts and his associates (48). Eighteen of 20 infected subjects gave specific complement fixation (51). McKee and her co-workers (229) used yolk sac harvest from chicken embryos infected with the virus of lymphogranuloma venereum in preparing an antigen for studying complement-fixation. Another source of antigen used by this group was infected lung of mice, which had previously been shown to be a potent source of antigenic material (326). In carrying out the test, the following reagents are essential: (a) the specific antigen; (b) human sera inactivated at 56°C. and diluted with isotonic saline; (c) complement from pooled guinea pig serum, and (d) indicator system made up of sensitized sheep erythrocytes. Controls for free complement and anticomplementary action of the reagents are included in every test run. Since the serum is diluted three times with saline, the lowest possible titer is 1:3, but the lowest usually tested by the investigators was 1:6.

1. Complement-fixation as a Diagnostic Aid: A few sera from known lymphogranulomatous patients gave good fixation with yolk sac antigen, but failed to react with mouse lung antigen (286). It was suggested that the lower titer of virus concentration in the lung tissue was responsible for the phenomenon; and, hence, the yolk sac antigen is preferred. In 48 sera tested from persons with clinical manifestations of the infection, or with positive Frei skin tests, all fixed complement with viral antigens, and failed to fix it with control preparations from respective normal tissues. In 41 instances, the complete fixation took place with serum dilutions between 1:15 and 1:600. No correlation between serum

titers and intensity of Frei reaction was recorded. In 30 cases from supposedly non-infected subjects, 28 failed to fix complement, and 2 gave low titers. Grace (111) reported positive results in 90 per cent of cases with clinical lymphogranuloma. Shaffer (327) reported that 113 of 115 patients with clinically recognizable lymphogranuloma had positive complement fixation tests. The other two were also Frei negative. The test may be considered of diagnostic significance when positive in serum dilutions of 1:6 or greater, according to Harrop and his associates (146). The objection has been raised that the complement fixation by the antigen of lymphogranuloma may be a biologically false test (183), due to the presence of reagin (because of syphilis infection). This challenge has been met by Grace and his group (118), who studied sera from 60 cases of presumably acquired syphilis and found that only 8 gave positive fixation for lymphogranuloma. In two syphilitic individuals with high titers of complement-fixing antibodies for lymphogranuloma venereum virus, the titers were not reduced by absorption with syphilis flocculation antigen. When the sera of 34 patients with congenital syphilis were tested against the antigen of lymphogranuloma, only two positive reactions were obtained. In both cases, it was suspected that the diseases existed concurrently. The authors concluded that a positive complement-fixation test implies a previous infection with the virus regardless of the presence or absence of syphilis.

2. *Appearance Time of the Complement-fixation Property:* From a case of accidental laboratory infection (147), Harrop observed that the complement-fixing properties appear in the serum within one week after the onset of symptoms, and this test remained positive after the Frei test had reverted to negative following a course of chemotherapy. In a well studied case, Sabin and Aring (309) noted the appearance of a positive complement-fixation test that titrated at 1:240 prior to the appearance of a positive Frei skin reaction. Grace (111) had detected antibodies in the sera of patients about one month after onset of infection.

3. *Significance of the Complement-fixation Test:* A positive complement fixation test has only the same significance as a positive Frei reaction, suggesting past or present infection, but not proving the lymphogranulomatous nature of the presenting lesion. One difficulty in the use of this reaction as a diagnostic criterion lies in the fact that numerous cross-reactions may result with psittacosis, syphilis, meningo-pneumonitis, trachoma, atypical pneumonia, inclusion blennorrhea and other diseases. These infections do not constitute a problem in differential diagnosis, except in rare instances. Levine and his associates (211) observed that 11 patients with pneumonia had positive complement-fixation tests, some with titer as high as 1:160. Three patients had complement-fixation tests as high as 1:64, but the Frei tests in these patients were negative. The authors conclude that, since cross-reactions were demonstrated from the antigens of lymphogranuloma and psittacosis agents, fixation must be corroborated by a positive Frei test before the diagnosis of lymphogranuloma can be made.

C. Inverted Frei Test

In 1932 Ravaut (290) demonstrated that purulent material from an infected case of lymphogranuloma will induce a positive skin reaction in a Frei reacting patient. Tissue from the suspected lesion is removed, and then inactivated by heating and prepared as an emulsion, prior to intradermal injection. A positive response is considered evidence that the lesion contains the agent of lymphogranuloma. The procedure is used commonly, and is frequently referred to in the section on "Clinical Manifestations." This diagnostic method is simply and usually a very valuable adjunct. Objections may be raised against the use of the inverted Frei test because (a) the infectious agent (or some other, as tubercle bacilli) may be incompletely inactivated and hence inadvertently introduced to the recipient; and (b) if both donor and recipient should, perchance, have some other infection, such as chancroid, the test will be positive, but will necessarily be falsely interpreted, since neither may have lymphogranuloma venereum. If anergy be suspected, this procedure is especially valuable (268), (310).

D. Intravenous Frei Reaction

In 1936, Hellerström (155) pointed out that patients with lymphogranuloma, even of many years duration, develop a febrile response with elevation of temperature of 1° to $1\frac{1}{2}^{\circ}\text{C.}$, ten to twelve hours following an intravenous injection with 0.25 to 0.5 cc. of modified Frei antigen. Ordinary antigen is diluted 8 times and heated for two hours at 60°C. After repeated injections of this antigen, the fever peaks diminished until finally no increase in temperature occurred. This observation was subsequently verified by Gay-Prieto in three patients with enlarged inguinal nodes (104). Intravenous injections with antigen prepared from virulent monkey brain induce hyperpyrexia up to $1\frac{1}{2}^{\circ}$ to 3°C. after twelve to eighteen hours, according to Ravaut, Levaditi and Maisler (291). The injections induced symptoms of toxemia similar to those found during the acute infection. Two patients with negative Frei cutaneous reactions prior to intravenous injections developed skin sensitivity. Morris and Canizares (249) reported that 23 of 24 patients with lymphogranuloma gave positive responses, as evidenced by elevated temperature to intravenous injections of mouse brain antigen, and 24 control patients did not respond. When antigen prepared from infected yolk sac of chicken embryo was used, only 11 of 24 patients gave thermal responses. These investigators believe the test is of diagnostic value when the mouse brain antigen is used. Robinson (299) has found the test disappointing, and feels that the injection of a foreign protein may induce a febrile response so frequently that the method is of limited worth.

E. Histopathology

Although the tissue response to invasion by the agent of lymphogranuloma venereum tends to follow a definite pattern, it should be emphasized that the microscopic appearance is not pathognomonic. The conservative pathologist reports that the appearance of the tissue is consistent with, but not diagnostic of, this infection.

F. Demonstration of Neutralizing Substances in Patient's Serum

Levaditi and his collaborators (202) demonstrated the presence of neutralizing substances in the sera of patients exhibiting evidence of infection with lymphogranuloma. The details of this study are described in the section on "Immunologic Studies."

1. *Mouse Protection Test:* Recently, Rodaniche (302) has described her experience with this procedure. If serum from a patient with lymphogranuloma venereum is incubated with virulent mouse brain emulsion for one-half hour at 38°C. and then for an additional fifteen hours at icebox temperature, the mixture will no longer produce meningo-encephalitis on intracerebral inoculation in the mouse. This experiment demonstrates the presence of neutralizing antibodies for the infectious agent in the serum of the patient. Rodaniche tested sera from 9 Frei-positive individuals exhibiting active symptoms believed to be induced by the agent of lymphogranuloma. In 8 of these she was able to detect neutralizing bodies.

2. *Guinea pig skin test:* When virulent mouse brain emulsion is inoculated intracutaneously in a guinea pig, a papule appears in two or three days, attains maximum size on the sixth day, and spontaneously regresses after two or three weeks. If the antigen is first incubated with sera from a patient with lymphogranuloma, as described above, the papule does not appear, because of the neutralizing effects of specific antibodies (361). Rodaniche (302) employed this technique to demonstrate neutralizing bodies in 8 of 9 patients suspected of having the infection. The sera from several patients with negative Frei tests likewise possessed the power to attenuate the viral agent. This test is not specific, since sera from normal individuals are able to prevent the appearance of the papule. If the papule should appear after incubating infectious material with serum from a patient who is suspected of having lymphogranuloma, it may be concluded that the diagnosis is incorrect.

G. Isolation of the Causative Agent

If material from a suspect lesion is properly prepared and inoculated intracerebrally in mice with production of a characteristic meningo-encephalitis, and if extract of the mouse brain, inactivated and diluted, induces a positive skin reaction in known Frei reactors, this may be considered to establish the diagnosis of lymphogranuloma. Other agents may produce an essentially similar histopathologic appearance (90), hence it is necessary that antigen be prepared from mouse brain to complete this diagnostic procedure. This extensive study is not adaptable to routine use, but it is of value in studying bizarre or unusual clinical manifestation of the disease.

II. Conclusions

No one of the ordinary laboratory procedures outlined in the foregoing paragraphs permits a definite and categoric diagnosis that a given lesion is due to the agent of lymphogranuloma venereum. At best, it may establish the fact that the patient now has or once had the infection. Knott and his associates (183),

in a comprehensive study from this clinic, challenge the specificity of the diagnostic skin and complement-fixation tests. Some of their remarks include the following: (a) that almost one-half of a group of 44 patients with chancroid had either positive skin reactions or positive complement-fixation tests for lymphogranuloma; (b) that only 84 per cent of patients with clinical lymphogranuloma had positive Frei tests, and of the group only 7 per cent had positive complement-fixation reactions; (c) in 18 per cent of colored patients with other venereal diseases, one-third had positive evidence of skin sensitivity for this disease; (d) that 10 of 44 cases had transient biologic false positive reactions for syphilis. To interpret the first three findings in proper perspective, certain significant features of Knott's study must be borne in mind: first, that the material was gathered from a venereal disease clinic whose population is 90 per cent colored, and where factual data are difficult to obtain since the patients are prone to overlook small and painless lesions; and, second, that not a single false skin reaction or complement-fixation test was detected among the control group of 20 members of the clinic personnel.

Nevertheless, although the above analysis will prove provocative and disconcerting to some, it must be emphasized that the final criteria in establishing the diagnosis of lymphogranuloma venereum depend on consideration of the history, appearance of the clinical manifestations, and careful evaluation of the laboratory data.

VIII. DIFFERENTIAL DIAGNOSIS

A. Diseases Associated with Genital Lesions

1. *Introductory Remarks.* The diagnosis of diseases of the external genitalia depends primarily on laboratory studies, secondarily, on historical data, and lastly, on the appearance of the lesions. Interpretation of serologic and skin tests should not be undertaken by the uninitiated. Knott and his associates (183) observed that one-third of the cases of lymphogranuloma venereum and chancroid during their early phases are associated with biologic false positive tests for syphilis. These are usually of low titer, transient, and spontaneously revert to negative. Hence a "typical chancre" of syphilis may be caused by the streptobacillus of Ducrey, or the virus of lymphogranuloma venereum. When the diagnosis is in doubt, it is better to wait and observe the effects of time on the serologic and skin reactions, and to withhold treatment. A positive Frei reaction does not imply that the lesion under observation is caused by lymphogranuloma, but only that the patient has, or once had, infection by the virus. Similarly, a positive Ducrey test implies either present or previous chancreoid infection. If the patient develops a positive skin reaction or serologic test, and these tests become more strongly positive under observation, this evidence is strongly suggestive that the presenting lesion is related to the laboratory procedure under consideration.

2. *Syphilis.* (a) *Early Syphilis:* The primary lesion of syphilis is usually elevated, firm, flat, and clean; but, if ulceration occurs, it may simulate the "chancre" of lymphogranuloma venereum. Unilateral edema of the labia with

ulceration is not uncommon, and is similar in appearance to esthiomène. Acquired syphilis is associated with vesicle formation with excessive rarity, if at all, and hence a herpetiform lesion practically excludes this disease. Darkfield examination is mandatory for every genital lesion, and, even if it fails to reveal *treponema pallidum*, a steadily increasing titre in the serologic series is confirmatory evidence for syphilis.

(b) *Late Lesions:* Gumma of the external genitalia is very rare in women. A localized, necrotic, ulcerated, painless lesion in a man with a history of syphilis and a positive serologic test suggests a gumma. The lesion will show evidence of healing after one or two injections of an arsenical. Biopsy study is of assistance.

3. *Chancroid.* Soft chancre is more apt to be confused with lymphogranuloma, since the initial lesion may be a vesicle. In chancroid, the ulcerated form is usually extensive, granular and painful. Multiple sores are common. Smears may reveal the Ducrey streptobacilli which are Gram-negative rods arranged in long curving chains. The diagnostic clue is a positive skin reaction induced by injecting intradermally bubo pus from a patient known to have chancroid, as advocated by Cole and Levin (39); or by injecting an antigen made from a culture of the Ducrey organisms (312), as described by Greenblatt and Sanderson (134).

4. *Granuloma Inguinale.* This venereal infection is primarily a disease of the skin in which the initial lesion is described as a cherry red area, in contrast to the beefy red of the syphilitic chancre (25). The superficial destruction rapidly spreads to involve the labial folds and extends toward anus and inguinal regions. In the male, the skin of the penis is denuded and the process soon includes the suprapubic area. The lymph nodes are not infected, but "pseudo-buboes" form as described by Greenblatt and his co-workers (133). The infection is one almost exclusively of Negroes, and the diagnosis is based on the finding of Donovan bodies on smear (66). They may be found by curetting the raw surfaces and staining with Wright or Giemsa stains. The bodies are arranged in diploform, are about the size of the pneumococcus, and have a clear zone about them, or occasionally a capsule. There is a pungent odor characteristic of the disease, and when this is once appreciated, the diagnosis is readily suspected.

5. *Herpes Progenitalis.* The vesicles of this process are similar to the herpetiform lesions of lymphogranuloma venereum. The disease is associated with a history of cyclical occurrence, unrelated to sexual exposure and with spontaneous remissions. The etiologic agent is a virus.

6. *Ecthyma of the Vulva.* The patient complains of multiple pustules with areas of ulceration of the labia. There may be extensive edema and hyperemia, as in esthiomène. According to Robinson (300), staphylococci and streptococci may be isolated. The lesions respond to aseptics, as gentian violet or sulfonamide ointments.

7. *Tuberculosis.* Tuberculosis of the external genitalia is seen with increasing rarity in either men or women, and is usually associated with infection of the internal genitalia. Stevenson (341) found only one primary case of infection of

TABLE 2
Differential Diagnosis of Inguinal Buboes

DISEASE	PRESENCE OF GENITAL LESION	RATE OF DEVELOPMENT	EXTENT OF INVOLVEMENT	CONSISTENCY OF NODES	CHARACTER OF PUS	SKIN REACTION	RATE OF HEALING	PAIN
Lympho-granuloma venereum	usually not seen	quite rapid	several nodes in a cluster, often bi-lateral	matted and soft; later mushy	thick creamy pus	multiple sinuses appear	slowly, many months	usually quite painful
Syphilis	usually present	moderately rapid	multiple bilateral	firm and rubbery	none	none	rapid	none
Chancroid	usually present	very rapid; one week after exposure	single node or group, uni-lateral	soft during entire infection	tenacious often blood-tinged	acute with crater-like slough	rapid	often very painful
Granuloma inguinale	very extensive	"pseudo-buboes," appear 1-2 mo. after exposure	extensive inguinal involvement	minor involvement	superficial ulceration	primarily skin infection	very slow	very painful
Tuberculosis	none	slow, indolent, chronic	multiple nodes, usually bilateral	varies, areas of softening and firmness	slowly oozing, thick	one or more sinus tracts	very slow	painless
Neoplasms	none unless secondary to genital cancer	slowly, usually months	usually unilateral	stony hard	none	usually none	fails to heal	painless

the labia in 18 studied. In the male, infection of the urethra follows kidney and bladder involvement. Diagnosis depends on histopathologic study, or isolation of the bacillus.

8. *Fungus Infections.* *Monilia albicans* can cause erythema and inflammation of the vaginal walls indistinguishable from other forms of elephantiasis. White plaques are found on the interior of the vulva, and from these the fungus may be cultivated on Sabouraud's medium. The lesion is identical in etiology and appearance to thrush. The causal relationship was demonstrated by Hesseltine and his group (161). It is most commonly found in diabetes mellitus, and responds to 5-10 per cent gentian violet applications.

9. *Neoplastic Diseases.* (a) *Benign Tumors:* Leiomyomata or cysts of the vagina are uncommon. Wharton reports that tumors occurred 260 times in 47,500 pathologic surgical specimens studied at Johns Hopkins Hospital (359). They are unilateral discrete structures, usually slow growing and unrelated to sexual behavior. Benign tumors of the male genitalia are rare.

(b) *Malignant Tumors:* In either sex, cancer is found in the older age group, in males, over 40, and in females, over 60. In women, concurrent leukoplakia is the rule. The majority of cases are epidermoid, slow growing, with relatively little edema, characterized by weeping necrosis and induration. Cancer and esthiomène have been observed co-existing (130), (138). Whenever malignant tumor is suspected, other diagnostic aids should be suspended until a biopsy is done.

B. Diseases Associated with Inguinal Adenopathy

Certain characteristics of lymph nodal changes may aid in the differentiation of lesions in the inguinal area. There is considerable variation in the process of invasion, but a general pattern evolves for each entity. This scheme appears as Table 2.

IX. LABORATORY FINDINGS

A. Blood

1. *Cellular Elements:* Chevallier and Bernard (34) have found a diminution in the erythrocyte count during the infectious period. This was likewise the experience of Wassén (361), who found the total cells fluctuated between 3.5 and 4.0 million. This has not been the observation of others (59).

There is usually an elevation of the leukocytic series, with total cells varying between 10,000 and 20,000. Ravaut, Bouline and Rabeau (289) found that the monocytes were increased to 17 per cent; Chevallier and Bernard (35) found an eosinophilia of 5 per cent; Gay-Prieto (103) found monocytic cells made up 20 per cent of total counts of about 15,000; Wassén (361) reported a leukocytosis of 10,000 to 20,000, noting this rise accompanied glandular involvement; Nicolau (256) observed extremes of 8,000 and 27,000; and Coutts (44) reported eosinophilia as high as 32 per cent, and found a less degree commonly.

2. *Chemical Changes:* In 1936, Gutman and his associates (137) reported that 26 of 35 patients with lymphogranuloma had elevated serum proteins. The

concentration usually exceeded 8.0 grams per cent with primary increase in the globulin fraction. Further fractionation revealed that this hyperglobulinemia depends on both increased euglobulin and pseudoglobulin. Howard and her group (166) observed hyperproteinemia, with reduction in albumin and increase in globulin, reversal of the albumin-globulin ratio, in both recently infected cases and those with active chronic lesions. Active syphilis tends to accentuate these findings, according to these investigators. Because the proteins approach normal with healing of lesions, they feel that such determinations have a prognostic value. In this clinic, Schamberg (315) found variations in proteins paralleled improvement in clinical status in 20 patients with acute infection. Of 67 cases studied by Kampmeier and his group (178), 62 showed total protein determination of more than 8.0 grams per cent and globulin of more than 3.0 grams per cent. No patient had a total protein of less than 7.5 grams per cent.

TABLE 3
Conditions Associated with Increased Blood Proteins

FREQUENTLY ASSOCIATED WITH HYPERPROTEINEMIA	INFREQUENTLY ASSOCIATED WITH HYPERPROTEINEMIA
1. Lymphogranuloma venereum	1. Metastatic bone lesions
2. Dehydration	2. Malaria
3. Secondary syphilis	3. Still's disease
4. Military tuberculosis	4. Rheumatoid arthritis
5. Multiple myeloma	5. Early portal cirrhosis
6. Leprosy	6. Leukemia
7. Trypanosomiasis	7. Filariasis
8. Kala-azar	8. Erythema induratum
9. Schistosomiasis	
10. Boeck's sarcoid	
11. Subacute bacterial endocarditis	
12. Disseminated sclerosis	

Since serum proteins may be increased in many other conditions, this determination is of minor value as a diagnostic aid. If hypoproteinemia is present, this mitigates against the diagnosis of lymphogranuloma venereum. Below is listed a table, modified from Shulman and Jeghers (330), enumerating many of the entities in which the blood proteins are increased.

It is a well known fact that sedimentation rate and formol gel determinations vary as the blood protein. Elevated sedimentation rate is common in lymphogranuloma according to Ferrari (75), and this increases with the proteins and not with the intensity of the illness. Schmidt (317) tested 40 infected individuals and found 36 had a rise in sedimentation rate, especially marked during the phase of greatest bubo involvement. When 1 cc. of serum is shaken with 2 drops of 40 per cent formol and allowed to rest at room temperature for 24 hours, an opaque gel mass forms. This formol-gel reaction is found to be present frequently in patients with lymphogranuloma (217).

A detailed study of chemical changes of the serum in lymphogranuloma ven-

creum has been made by Rosen and his collaborators (306), comparing these values to those found in normal individuals and to those found in patients infected with other venereal diseases (307). Table 4 is modified from the first of these papers.

B. Serologic Tests for Syphilis

Observation that biologically false positive reactions for syphilis are common in patients with lymphogranuloma, was first recorded by Ravaut and Rabreau (293). Because of the presence of a high serum globulin, false Wassermann reactions and also anticomplementary reactions are common. Knott and his collaborators (183) from this clinic report that one-third of patients with early infection have transient false positive reactions for syphilis.

C. Urine

In those cases in which there is direct infection of the urethra or bladder, it is apparent that leukocytes, albumin and desquamated epithelial cells will be

TABLE 4
Serum Changes in Lymphogranuloma Venereum

	INFECTED PATIENTS	NORMAL CONTROLS
	mg.	mg.
Total lipids	1,401 \pm 41	1,621 \pm 32
Cholesterol	180 \pm 10	228 \pm 6
Lecithin	169 \pm 7	200 \pm 3
Lipid phosphorus	6.8 \pm 0.3	8.0 \pm 0.1
Free cholesterol	75 \pm 3	76 \pm 3
Globulin	3.84 \pm 0.21	2.28 \pm 0.04
Albumin	4.01 \pm 0.12	4.38 \pm 0.04

common in the urinary sediment. However, when there is no apparent invasion of this sort, traces of albumin have been detected by Gutman (136). To our knowledge, no other abnormality in the urinary excretion is reported.

D. Cerebrospinal Fluid

No abnormality of the spinal fluid was reported by Ravaut and Scheikevitch (291), or by D'Aunoy and von Haam (141). Chevallier and Bernard (36) found increase in protein on one occasion, and Midaña and Vercellino (239) found the same deviation from the normal in 2 out of 11 cases. Kitigawa (179) claimed that increase in tension is not uncommon. Isolation of the agent is described in the section on "Clinical Manifestations".

E. Stools

Examination of stools in cases of proctitis or rectal stricture reveals the presence of pus and either gross or occult blood. According to Gray (126), lymphogranuloma is not seen in North China; but *Schistosoma japonicum* as a cause of

rectal stricture is not uncommon, and hence stools must be examined for the eggs of this parasite.

F. X-ray Studies

Rendich and Poppel (297) have reported that in three cases in which lymphogranulomatous infection of the colon was suspected, a characteristic x-ray picture was obtained. This consists of smoothing of the usual relief, and a scallop-like appearance, which the authors refer to as "indenture pattern". In a review of 500 cases of ulcerative colitis, Weber and Bargaen (362) found three that they believed fitted into this group. All patients had involvement of lower sigmoid colon and rectum, and a history of lymphogranuloma. The x-ray showed shortening and narrowing of the segments. Studies of the mucosa revealed absence of relief or deeply pitted pattern. The authors felt that this is fairly typical.

X. TREATMENT

A. Introduction

Prior to the advent of the sulfonamides, various medical and surgical procedures were tried for the treatment of the numerous manifestations of lymphogranuloma venereum, with varying degrees of success. Many of these are now only of historic interest; others are adaptable as adjuncts in modern therapy. Sensitivity to sulfonamides is becoming increasingly common, since some patients who were treated for the first time without developing toxic manifestations have, on subsequent courses of the drug, exhibited symptoms of intolerance. It is for this reason that other therapeutic measures must be considered and evaluated.

B. Prophylaxis and Isolation

1. *Prophylaxis* Except for the occasional instance of accidental inoculation with a contaminated surgical instrument, and the several infections among laboratory workers, and the few references to the disease in children probably transmitted by contaminated enema tips and similar devices, no case of non-venereal adult infection is reported. Hence, except for the obvious precautions that should be taken to prevent such infections as mentioned above, prophylaxis consists in preventing sexual contact between infected and non-infected individuals. This cannot be done until case-reporting and case-finding methods are adopted. Because the initial genital lesion is minute and transient, and the period of tubercle formation so variable and prolonged, the difficulties inherent in this control are apparent. Until studies are undertaken, their practicability cannot be predetermined. Frei (97) has recently suggested isolating men with anorectal lesions since one must suspect these patients of pederasty and as potential sources of infection when housed with other males. He further recommends routine skin-testing of all persons with even mild symptoms of proctitis.

2. *Isolation*: How long should a patient with infectious lesions be isolated? As yet this question remains unanswered. In institutions as the Armed Forces

where isolation is mandatory for all venereally infected members, it is recommended that patients be retained until genital lesions heal, or, in the case of inguinal adenopathy, until the patient has completed one full course of sulfonamide therapy. Men with anorectal lesions should be questioned concerning homosexuality, and be handled accordingly. Since esthioène has not been proved infectious, women with this manifestation need not be hospitalized.

C. Therapeutic Measures, Excluding Sulfonamides

In evaluating any therapeutic measure, it is necessary to bear in mind the tendency for lesions to heal spontaneously (24). The initial lesion requires no therapy, and the inguinal nodes usually undergo scarring following suppuration. The chronic lesions of genital elephantiasis and anorectal involvement do not heal without intervention.

1. *Topical Applications:* Greenblatt and Wright (135) recommended that ulcerated genital lesions be treated with neoarsphenamine in glycerine for the relief of symptoms associated with secondary fusospirochetosis. Pain caused by distention of the inguinal nodes often responds to an ice-pack.

2. *Excision of Nodes:* Klotz (182) recommended complete removal of the infected nodes as an effective means of therapy. Others have found incision and drainage satisfactory. Partial adenectomy was employed by D'Aunoy and von Haam, who observed healing of the lesions one month after operation in 50 per cent of the cases. Simple incision with drainage prolonged recovery as a rule.

3. *Vaccine Therapy:* Gay-Prieto (104) described improvement following subcutaneous inoculations with Frei antigen in patients with early lesions. Others (153), (1) found this form of therapy of value. However, Brandt and Greenblatt (26) reported favorable results during the early stages with bubo involvement, but were disappointed with the response of ulcerations of the genitalia and also of anorectal lesions. Prehn (276) found that intracutaneous administration of graded doses of potent Frei antigen every other day until at least eight doses or more are injected near the site of lymphadenitis seems to bring about rapid involution, absorption and cessation of drainage. Anderson and Harmon (1) treated 28 cases with diluted Frei antigen, and reported satisfactory results.

Autoserum as Specific Antigen: It is the impression of Marks (223) that the serum of infected patients contains the antigen of lymphogranuloma and that by injecting the patient's own serum intramuscularly the patient will build up antibodies which have therapeutic value. To test this theory, he treated 50 patients, 35 of whom had rectal lesions, by inoculating each patient with first 0.5 cc. of his own serum and gradually increasing the dose until 7 cc. were given, every four days for a course of 12 injections. According to the author, every lesion improved, with relief of pressure, diminution of rectal discharge, and lessening of pain.

4. *Intravenous Vaccinotherapy:* Hellerström (155) reported that intravenous injections of Frei antigen into patients with lymphogranuloma induced high fevers with subsequent improvement in the clinical course. Kornblith (189)

found this an effective form of therapy in a large series of cases; but Greenblatt and Brandt (132) found immediate exacerbation of symptoms following intravenous injections of mouse brain antigen, with favorable results in only two of eight cases. Because of the inconvenience, expense, and the questionable merits, this form of treatment is not recommended.

5. *Immune Transfusions*: By giving blood transfusion totaling 300 cc. from individuals recently recovered from the early stages of the disease, Brady (22) claimed symptoms were greatly reduced in 16 patients with bubo involvement. Following this therapy, 11 of the patients experienced a febrile response lasting 2-4 hours, but this was replaced by improvement in attitude, color, appearance and weight.

6. *Physiotherapy*: Several forms of physiotherapy have been advocated.

a) *X-ray*: Martin and de Lorimer (226) administered 50 to 100 r. to 61 cases with inguinal adenopathy over a period of one to three months. With the exception of two cases, all responded satisfactorily; and the authors felt that roentgen therapy is superior to all other forms except sulfonamide therapy, and recommend it for those patients unable to tolerate the drugs. Brandt and Greenblatt (26) experienced disappointment with this treatment, admitting that it hastens suppuration, but that the final results are not comparable to either chemotherapy or vaccinothrapy.

b) *Long Wave Diathermy*: Martz and Foote (227) used diathermy in five cases with rectal stricture, beginning with 900 milliamperes and increasing to 1800. They used metallic Hegar dilators as electrodes, and administered Frei antigen concurrently. They thought the patients had relief of pain, discharge and tenesmus, but the stricture was uninfluenced.

c) *Short Wave Diathermy*: In 1935, Bensaude and Lambling (16) reported that diathermy reduces congestion and promotes healing in proctitis when given for twenty minutes two or three times weekly for a total of 10 to 12 applications. Temporary relief following short wave therapy was noticed by Shackelford and Weinberg (322), but these workers ascribe the improvement to the use of dilators inserted into the rectum several times weekly, rather than to the action of the diathermy. Relief of pain was experienced by patients with genital ulceration and urethral stricture when this form of treatment was administered (26).

7. *Antimony Compounds*: Shaffer and his associates (324) treated eight patients with inguinal adenopathy and four with the anorectal syndrome, with anthiomaline (lithium antimoniothiomalate), a trivalent salt of antimony. They gave intramuscular injections 2-3 times weekly until 2-4 grams of the drug were given during each of two courses. Patients with the inguinal lesions responded within one month, and were cured within 5-7 weeks; whereas the other four patients noted diminution in signs of proctitis without any change in the strictures. In a subsequent study, the authors (323) found that 10 of 13 cases experienced improvement in rectal symptoms.

Law (194) treated 33 European and 187 African soldiers with lymphogranuloma venereum. In these men the Frei test was positive in 61 per cent of the cases, and in the remainder, was doubtful, negative or not done. The patients were

treated with anthiomaline, given intramuscularly or intravenously. The initial dose was 0.5 cc. and each subsequent injection was increased by this amount until a dose of 2.0 cc. was reached. A total of 20 injections were prescribed which permitted about 0.2 grams of antimony metal for each patient. The author found that this therapy induced healing in three weeks, and is equal in efficacy to a course of 50 to 100 grams of sulfanilamide.

8. *Surgical Repair*: It has been customary to remove polypoid vulval growths by surgical means and to perform plastic repairs on elephantiasis of the genitalia in both sexes. Such procedures have been unsatisfactory because of the friability of the tissue. Many cases of stricture required colostomy, and as recently as 1941 a mortality of 14 per cent was reported by Barker and Murphy (7) in those instances where colostomy was followed by sacroperineal resection of the infected tissue. Morris (250) also found it necessary to do combined abdominoperineal resections when the infection extended to the sigmoid colon. Such elaborate procedures are unavoidable when extensive bowel tissue is involved.

D. Experimental Sulfonamide Therapy

In 1938 Levaditi (201) showed that sulfanilamide administered orally to mice prevents the meningo-encephalitis otherwise induced by intracerebral injection of the lymphogranuloma venereum virus. This work was substantiated the same year when MacCallum and Findlay (219) reported that, in a group of mice treated with sulfanilamide following intracerebral inoculation of the virus, only a few animals developed symptoms of meningo-encephalitis, while most of the untreated controls died. Mice, inoculated with an emulsion of infected mouse brain from animals previously treated with sulfapyridine, nevertheless developed mild infections, not sufficiently severe to cause death according to Schlossberger and Bär (316). This suggests inhibition of the virus by the drug, but without loss of infectivity. Prontosil album has essentially the same effect, causing amelioration of symptoms in infected mice, but without effecting any complete cures (6). Findlay (79), (80) was able to reduce the mortality by feeding sulfonamides in gum acacia to mice previously inoculated with virulent material. He found that the drugs varied in protecting power, in the following descending order: sulfamethylthiazole, sulfapyridine, sulfathiazole, and sulfanilamide. Jones and her associates (173) confirmed this report, noting that sulfadiazine, sulfathiazole and sulfaguanidine are capable of preventing death from acute infection with the virus when given prophylactically, and equally effective when administered therapeutically. The mice were not entirely symptom free, and, when the animals treated with sulfaguanidine and sulfathiazole were sacrificed, re-inoculation of the mouse brains into yolk sacs of chicken embryos produced some growth, suggesting that the drugs are virostatic but not virocidal. Callomon and Brown (29) corroborated much of this work, by showing that when mice, injected intracerebrally with the virus, are fed sulfonamides, the same order of protection occurred: namely, sulfathiazole, sulfapyridine, and finally, sulfanilamide and neoprontosil. When treated and untreated animals were killed, histologic studies of the brains revealed that the amount of cellular infiltration was

equal in the treated, asymptomatic mice and in the obvious sick animals. Usually the meninges were infiltrated, and occasionally the cells, consisting of neutrophilic leukocytes, lymphocytes and plasma cells, were found in the brain substance. When treated animals that survived the first inoculation were re-inoculated with a virulent agent, very few died. From this, it was assumed that the first infection had induced immunity.

According to Holder and his associates (164), when the virus of lymphogranuloma is incubated with sulfadiazine, sulfathiazole and sulfanilyl sulfanilate, and sulfaguanidine for varying periods from two to twenty-four hours, the agent is not destroyed but its virulence reduced, with the drugs most efficient in the order named. When the agent was re-injected into mice after contact with sulfonamide drugs, there was prolongation of the incubation period and also of the duration of symptoms.

All these studies suggest that, although the sulfonamides are able to prevent death of the animals, it does not mean the viral agent is destroyed. Jones (173) warns that the significance of this finding in terms of human infections is of prime importance, since a period of latency may be induced by the drug therapy, or perhaps even a carrier state may be effected.

E. Current Therapy of Specific Lesions

1. *Early Lesions:* For the most part, the initial lesion does not constitute a therapeutic problem. In the male, the lesions usually heal spontaneously and in most instances are overlooked by the patient. Coutts (45) recommends treating vulval ulcers with 5 per cent sulfathiazole ointment, with the addition of female sex hormone in persistent cases. Patients seek medical assistance because of inguinal involvement, and often not until the nodes are painful or have already suppurated. Treatment of infected nodes does not depend on the location of the adenopathy. Excision is neither necessary nor recommended. Severe tension may be relieved by aspiration. Hamilton (144) obtained immediate resolution of lymphadenitis in 13 of 15 cases by administering sulfanilamide for about fifteen days. Stein (340) treated 35 cases with the bubonic form of lymphogranuloma with the same drug and advised continuation of therapy for at least a week after the lesions have subsided. After six months 20 patients remained well, and in 4 cases the Frei reaction had reverted to negative. Schamberg (315) noted immediate subjective improvement in 20 colored patients, but objective evidence of response to sulfanilamide was slower. Prats (275), Trautman and Thomason (355), Graham (125) and Grace (123) found this drug satisfactory. Recently Noojin and his associates (258) report that in their hands sulfathiazole and sulfadiazine are equally efficacious in preventing suppuration and promoting resolution of infected inguinal nodes.

In this clinic the current procedure is to prescribe one gram of sulfathiazole (or sulfadiazine) orally four times daily for two weeks. If the patient tolerates the drug without reaction, treatment is continued with 3 grams daily for an additional two or three weeks, depending on the involution of the adenopathy. This routine has proved satisfactory, and, with this dosage, toxic manifestations

are exceedingly rare, even though patients remain ambulatory. The constitutional symptoms respond within two days, and, although there may be no apparent change in the adenopathy, the patients report alleviation of pain within this interval. When therapy is continued for four to five weeks, recurrences are not seen. It is too early to report on the effect this program will have on the prevention of late manifestations of the disease, and we are unable to evaluate the influence of sulfonamide therapy on transmission by sexual contact. The above treatment for 4-5 weeks constitutes one course.

Sulzberger and Baer (348) caution that in evaluating any therapy for lymphogranuloma venereum, it should be borne in mind that the early manifestations often subside within a few weeks, either spontaneously or under such simple care as bed rest and hot compresses. It is the impression of Sulzberger (347) that the therapeutic efficacy of the sulfonamides, in acute lymphogranuloma venereum has not yet been proved; and that in his experience, hospitalized cases respond in approximately the same period without specific chemotherapy.

2. *Ophthalmitis*: A case of a 39 year old white man who developed purulent conjunctivitis is reported by Curth and his associates (57). Within one year the cornea became opaque and vision was lost. During the next few years, the conjunctiva of the opposite eye became inflamed and it was from this discharge that the virus was isolated. The patient was treated rigorously with sulfanilamide, with prompt abatement of the infection. Oliphant and his co-workers (259) described acute ophthalmitis in a laboratory worker exposed to the virus of lymphogranuloma. Pus from the conjunctival sac was inoculated intracerebrally in mouse brains with recovery of the agent. The suppurative process responded to sulfadiazine therapy, which was administered in doses of three grams daily for two weeks.

3. *Elephantiasis of the External Genitalia*: Prior to the advent of the sulfonamides, both patient and physician despaired of treating ulcerative lesions of the external genitalia. The small polypoid growths were removed surgically, but, if infection set in, necrosis of additional tissue often followed. Surgical excision was the only means of relieving suffering, and this was usually a temporary respite. In 1942, Kampmeier (177) noted that in some cases of esthiomène, rapid improvement followed the administration of chemotherapy. We have recently observed a patient with marked thickening and induration of the penis, in which we suspected that a cicatricial process had occurred because the history extended back three years. The patient was given sulfathiazole, three grams daily for three months, during which interval he experienced relief of pain and urinary symptoms.

If the lesion is of long duration, with infiltration and sclerosis, plastic repair is usually necessary. However, neither duration of symptoms nor firmness of tissue is any indication of the extent of fibrosis. Preliminary treatment with sulfonamides for several months is desirable, and the degree of thickening and induration may thereby be reduced. It is further recommended that drug therapy be maintained during the following operative intervention for any lesion involving the external genitalia.

4. *Anorectal Complications:* a) *General Measures:* Patients with anorectal involvement usually exhibit varying degrees of malnourishment and debilitation. This should be counteracted by supplementing the diet with foods high in protein and vitamin content. Additional vitamins are often valuable. Foods with low residue should be used if possible to reduce irritation of the parts, and lubricating products added to the daily intake. Anemia should be combated with ferrous sulfate. Not uncommonly the patient is depressed and discouraged, and needs assistance along these lines.

b) *Local Treatment:* Bacon and Griffin (4) recommend instillation of 10 to 20 cc. of a 25 per cent aqueous solution of ichthyol twice daily to soothe the mucous membranes. Irrigations with hot water or weak potassium permanganate and other mild antiseptics relieve tenesmus and act as cleansing agents. Application of 10 per cent silver nitrate or 50 per cent metaphen are of questionable value, but may promote healing of denuded bowel mucosa. Coutts (45) advocates 3 per cent sulfanilamide rectal enemas in a syrupy concoction. If stricture is present, 100 cc. of this is introduced above the ring by catheter, and a few drops of an opiate added to reduce tenesmus. After two weeks of this daily procedure, diathermy and dilation are begun.

c) *Specific Therapy:* In 1938, Shropshire treated 9 patients (329) with rectal stricture due to lymphogranuloma venereum with sulfanilamide. Sixty grams of the drug were prescribed for a thirty day interval. Proctoscopic study revealed that previously denuded bowel was covered by healthy mucosa, and the granulation tissue had been largely replaced. Symptomatically, most of the patients reported lessening of tenesmus, mucous stools, rectal discharge, and bleeding. Two additional patients with discharge from colostomy sites improved. The same year, Shaffer and Arnold (325) observed improvement in patients with this problem.

Hebb and his associates (150) from this clinic initiated intravenous therapy with sodium sulfanilyl sulfanilate and sodium sulfanilate for 14 patients with rectal stricture. Treatment was continued from six to thirty-five weeks resulting in cessation of local symptoms, improvement in general well-being, and often in absorption of the stricture and closure of fistulas. The explanation for the disappearance of the stricture depends on a proper understanding of the lesion. Much of the ring is composed of superficially infected and edematous granulation tissue, which may be replaced by normal mucosa. Further study (149) revealed that in four cases subsequent proctoscopic visualization showed no evidence of stricture; 12 patients had 75 per cent return to normal bowel function with an inconsequential fibrous band present, and 17 patients, or half of the group, showed various degrees of improvement with reduction in rectal symptoms with slight or no change in the stricture. It is now the impression of these authors (149) that oral therapy is equally effective, and they advocate maintenance of sulfadiazine therapy from six to twelve months with drug levels at 3-5 mgm. per 100 ml. of blood. As an additional measure, they advocate dilatation of the ring 2-3 times weekly. Palmer and his group (260) have reported some success with both intravenous and oral treatment, using the same drugs used by

Hebb. Proctitis without stricture may be entirely cured by continuous treatment with sulfathiazole, 3.0 to 4.5 grams daily, according to Grace (111). This worker recommends short rest periods between courses of chemotherapy, and during this interval he gives intravenous Frei antigen.

Seidenstein (318) has reported on the use of sulfanilamide given both orally and by enemas to patients with rectal strictures. Frei antigen was also given as an adjunct. In one case the stricture "melted" away entirely, yet reappeared in an adjacent portion of the rectum 21 months after cessation of therapy. In the four remaining cases of this series, all the patients have done well and surgical intervention was unnecessary. It is the opinion of the author that the sulfonamides are effective against the pyogenic secondary invaders, and because of the relapse in the first case cited, he suggested these drugs are ineffectual against the lymphogranuloma virus. Sulfaguanidine is but slightly absorbed from the intestinal tract, and hence is of great theoretical value in treating intestinal infections. Canizares and Morris (31) induced improvement in 6 cases of rectal ulceration with this drug, but could not influence stricture.

An illuminating study is presented by Levy (213) and his staff who compare the previous and recent methods of therapy. Among the former regimens, they include administration of intradermal Frei antigen and such surgical procedures as dilatation and colostomy. If the strictures were above the recto-sigmoid junction a permanent colostomy was done with removal of the infected bowel in a few cases. Dilatation or temporary colostomy was done depending on the degree of obstruction if the strictures were below this level. The results were unsatisfactory in most cases with the above forms of therapy, although 75 per cent of 150 patients treated required dilatation of the ring or more radical therapy.

The more recent series consists of 118 patients treated almost exclusively with sulfonamides. Only 4 subjects or 5 per cent of the group required dilation and in no instance was it necessary to resort to colostomy. The patients were given 5 grams of sodium sulfanilate for the first dose and then 1.5 grams daily thereafter. Within 3 to 4 weeks, the patients experienced amelioration of bowel symptoms and improvement in general health. The strictures decreased in size but if the rectal discharge persisted, sulfathiazole was given in addition to the sulfanilate for a few days with immediate relief. These patients have been treated for as long as several years without serious manifestation of drug toxicity and with continued well-being according to the authors.

d) *Surgical Procedures*: Indications for operative intervention according to Bacon (3) include the following: constrictions that have failed to respond to prolonged chemotherapy, annular or tubular strictures above the peritoneal reflection, as classified by Peyton (269), where obstruction is impending. Bacon feels that complete eradication is the procedure of choice, once the decision to operate is made. He advocates the abdomino-perineal resection, preferably done in two stages. In the preliminary step, a colostomy is done, usually in the left inguinal position. In the final maneuver, the perineal excision is carried out by removing the involved bowel with an adequate margin of healthy tissue above

the infection site. The author has performed this operation on 27 patients, and all are living and doing well. Morris (250) and Barker and Murphy (7) likewise recommend this extensive surgical procedure.

F. Evaluation of Treatment

It is apparent from the foregoing that the final chapter has not yet been written on the successful treatment of this disease. The value of the sulfonamides cannot be overestimated, yet evaluation of these chemotherapeutic agents is not complete. From animal experimentation it appears that these drugs are virostatic rather than virocidal.

There is a certain parallelism between the history of treatment of syphilis and of lymphogranuloma venereum. When arsenicals were first introduced in the treatment of syphilis, it was believed that one or at most several injections would eliminate the infection. It is now recognized that disappearance of the surface spirochetes and of the initial lesions do not constitute a "cure." The patient may remain infectious, and may subsequently develop manifestations of clinical syphilis. This suggests that proper interpretation of any therapeutic scheme in lymphogranuloma will necessitate long periods of observation, with re-examination of the patient at frequent intervals.

It is appropriate that we speak of "cure" in these infections using quotation marks to imply that the patient is clinically well rather than to imply complete eradication of the last remaining virus? Moore (248) describes a syphilitic patient as attaining clinical "cure" when he exhibits no clinical evidence of the infection; as attaining serologic "cure" when his serologic tests for syphilis are negative; and as attaining biologic "cure" when the last remaining spirochet is destroyed. The difficulties of arriving at the decision that a patient is unequivocally "cured" are apparent.

If the premise that a parallelism between these two venereal infections is justified, we must speak even more cautiously of "cure" in lymphogranuloma, since so little is now known about the natural history of the virus and the immunologic reactions it induces in the human host.

XI. SUMMARY

Lymphogranuloma venereum is a protean disease that, although observed and adequately described over a century ago, first attracted medical attention only in the past thirty years, when the pathologic aspects were re-defined. Not until the introduction of a satisfactory diagnostic tool, the Frei test, did clinicians become fully aware of the scope of this venereal infection. In a relatively short time the etiologic agent, a virus, has been isolated, its relationship to other human pathogens established, and a satisfactory therapeutic regime been propounded. At present, many clinical manifestations are ascribed to the causative agent, but from relatively few has the organism been recovered. There is no doubt that some of these entities will prove to be incorrectly associated with this disease, and, in all likelihood, hitherto unexplained entities may be shown to be initiated by the agent.

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THE LATE EFFECTS OF CEREBRAL BIRTH INJURIES

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CONTENTS

	<i>Page</i>
I. INTRODUCTION.....	71
II. SELECTION OF CASES.....	72
III. PATHOLOGICAL TYPES.....	73
IV. ETIOLOGICAL FACTORS.....	79
V. CLINICAL CONSIDERATIONS.....	85
VI. SUMMARY.....	91
VII. APPENDIX.....	94

I. INTRODUCTION

In his extensive study on birth injuries in 1926, F. R. Ford (1) pointed out that knowledge of the immediate effects of birth injuries is well established but "when we turn to the consideration of the late results of such birth injuries we find little exact information and the greatest difference of opinion." Although almost twenty years have elapsed since this publication, it still holds true that "there does not seem to be any general agreement among neuropathologists about the late pathological anatomy of intracranial hemorrhages." Ford's publication came at the end of an era of great interest in the problem of birth injuries and summarized many valuable contributions which had preceded his publication (R. Pierson (2) 1923, Crothers (3) 1923, E. Holland (4) 1922, Schwartz (5) 1922, v Reuss (6) 1921, Ylppoe (7) 1919). These papers added greatly to the knowledge of the mechanism of a birth injury and accumulated evidence that hemorrhages into the brain substance and the spinal cord play a major part as cause of death. In spite of these papers, however, many people seem to believe that a child injured at birth will either die or recover completely and very little is known about the permanent damage to the nervous system which follows a birth injury in those children who survive. There seem to be two main reasons for the present attitude. Many clinicians and pathologists think that congenital malformations are of greater importance than birth injuries and that most of the lesions which may be found in mentally defective children are the result of a pathological pre-natal development. It is true that if the number of mentally defectives as a whole is considered, a majority of cases is due to faulty prenatal development.

A clinical analysis of a material of 100 autopsies of mentally defectives, which was recently made by the author (8), has produced evidence that in the idiot group about 50% are due to congenital malformations but 30 to 35% do depend on vascular lesions developing at the time of birth. In the imbecile group the

number of birth injuries amounts to about 8%, while it is impossible to determine with any accuracy the number of high grade defectives injured at birth. A second reason for our lack of knowledge is the fact that no adequate method of research has been applied to differentiate the cases of congenital malformations from those due to birth injury. It is evident that many children of the former group are born under pathological conditions and that, therefore, a purely clinical approach would result in erroneous conclusions. In order to obtain satisfactory results, all cases of congenital malformations have to be excluded from such a study, even if sequelae of a birth injury are found in addition to the congenital malformation. Only an approach from various angles can render results which are beyond argument. It was the purpose of the following study to analyze a series of 100 autopsies of mentally defective patients after exclusion of all mongoloids, to determine the late effects of an injury at birth.

The term "birth injury" refers to all kinds of injury to the nervous system sustained in the process of birth. It is evident that the term does not imply any application of instruments or any faulty management on the part of the attending obstetrician. The term merely includes all cases showing evidence that some extrinsic factors related to the passage of the baby have interfered and produced results which affected the further development of the nervous system.

II. SELECTION OF CASES

In view of the fact that it is hard to establish a birth injury as a causative factor many years after birth, a special method had to be adopted for the selection of cases. The criteria used in the selection of the material may be summarized as follows:

1. Hereditary:

- a. All patients had normal parents and a negative family history.
- b. All children had normal siblings and were the only mentally deficient members of the family except for those few with no siblings.

2. Clinical:

- a. The physical examination of these children revealed no malformations or developmental disorders which would suggest a pre-natal disturbance. Early malformations rarely occur singly and a multiplicity of malformations strongly suggests pre-natal factors. The only abnormality found was that of a neurological character of central origin.
- b. Examination at the time of birth was apparently negative and no signs of microcephaly were present at that time. Microcephaly, if present, was evidenced in the majority of cases by a skull circumference of between 17 and 19 inches, indicating an arrest of development several months after birth. The circumference was never below $14\frac{1}{2}$ inches.

3. Pathological:

- a. Examination of the brain and spinal cord showed maturity of the central nervous system. No signs of pre-natal developmental disorders were found.

- b. The character of the lesions in birth injuries was such as to indicate that they were either the consequence of vascular incidents and depended in their distribution upon vascular patterns, or were caused by extrinsic agents which produced patchy devastation while the unaffected tissue was essentially negative.

III. PATHOLOGICAL TYPES

By the application of the criteria above mentioned, twenty four cases have been found in a material of 130 autopsies of mentally deficient children of various types which conformed to the standards previously set.

The lesions found in these cases may be divided into three groups. Group I Mantle Sclerosis, Group II Cystic Degeneration of the Brain, Group III Diffuse Patchy Devastation:

Group I. Mantle Sclerosis

This condition is also known under the names of granular or parchment atrophy of the brain, sub-cortical encephalomalacia, sub-cortical porencephaly.

The lesion in the brain consists of a degeneration of the cortical layers with necrosis of the sub-cortical white matter. The white matter may present a status spongiosus in which small sub-cortical cysts are sometimes found. The gray matter is devoid of nerve cells which are replaced by gliosis. The leptomeningeal covering of the affected areas is greatly thickened. The subarachnoid spaces are fibrotic and contain enlarged vessels suspended in the fibrous meshwork. The pia is greatly thickened and tightly fused with the gliotic cortex. There are areas of calcification and residuals of old and more recent hemorrhages. The condition may affect parts of one lobe or a whole lobe or even one hemisphere. The condition is asymmetrical, but may be bi-lateral. The distribution of the lesions indicates that their development depends upon lesions of the vascular tree. In some cases occlusion of branches of the main arteries is the cause. In some cases, venous thromboses and sinus thrombosis are suggested as causes. In at least three of five cases under study, the sagittal sinus was found fibrotic and obliterated with no or little canalization.

Data on five cases of mantle sclerosis are given in Chart 1. A more detailed description of Case 3 may serve as a demonstration for the whole group.

Both hemispheres revealed destruction of the occipital poles. In the left hemisphere the destruction was restricted to that area while on the right side the central region and parietal regions were also involved and destroyed to a large extent. The cortex appeared shrunken, most of the nerve cells destroyed and the remaining cells clustered together in small islands. These islands were separated from each other by strands of ingrowing mesenchymal scar tissue and glia strands. The white cores of the shrunken convolutions were spongy-like with most of the axis cylinders and myelin sheaths destroyed. Parts of the white matter showed definite cavity formation with mesenchymal organization and glia meshwork at the edge of the cavities. More centrally the white matter appeared demyelinated and showed a great increase in glia. The vessels showed perivascular fibrosis with some round cell infiltration in the perivascular spaces. The cavities were filled with gutter cells which appeared mulberry-like in the Nissl stain, but showed a definite cell character in phosphotungstic acid stain.

In this case, the lesion followed the distribution of the left posterior cerebral artery and

the right posterior and medial cerebral arteries. Only those parts of the right hemisphere were preserved which were supplied by the right anterior cerebral artery. In this case the sagittal sinus was not obliterated.

The right putamen showed a status marmoratus. This observation is of special interest for the pathogenesis of this much discussed condition. It may be remembered that in 1928 R. Morrison (10) found in dogs, whose cortex was removed experimentally, that the underlying basal ganglia developed status marmoratus. The lesion in Case 3 resembles Morri-

CHART 1
Manile sclerosis
(Pathology: Group 1)

CASE NUMBER	MENTAL STATUS AND SEX	AGE AT DEATH	BIRTH	EPILEPTIC SEIZURES	CLINICAL SYMPTOMS
		yrs.			
1 (3/11)	Idiot M	15	One of twins. Breech presentation.	Six convulsions at 18 months.	Listless. Helpless. Never walked or talked. Purposeless motions of hands. Rolled head.
2 (41/75)	Imbec. M	18	Six wks. premature. Instrumental. Cerebral hemorrhage 3 days after birth.	Not reported.	Slow development. Spastic paraplegia of legs. Slurred speech. Microcephaly (17½").
3 (42/98)	Idiot F	13	Full term delivery without physician.	Two days after birth, fits for 10 days. Crying spells. After 6 months, return of convulsions. Epilepsy at irregular intervals.	Spastic paraplegia of legs. Helpless bedridden. Osteomalacia. Microcephaly (17½").
4 (43/100)	Imbec. M	22	Full term, one of twins, other died.	Convulsions for several days after birth.	Right hemiplegia. Temper tantrums and epileptic seizures at irregular intervals. Slight microcephaly (19½"). Strabismus. Partial optic atrophy.
5 (43/109)	Idiot F	7½	Full term, instrumental.	9 days convulsions at age of 10 months. Some generalized some more unilateral with twitching of right face, arm, and leg. Crying spells and epileptic seizures at irregular intervals.	Opisthotonus, spastic extremities, helpless. Slight microcephaly (18½"). Ventriculogram: dilated ventricles with large defect in the right parietal region. Epileptic seizures in increased number with progressive mental deterioration and increasing spasticity.

son's observations and it seems as if Nature has repeated Morrison's experiment by natural destruction of the cortex through occlusion of the medial cerebral artery.

In addition to the findings described above, large areas of calcification were found in the sub-cortical layers. Besides the reactive inflammatory round cell infiltration in the white matter there was no indication of encephalitis in this case. Cases 4 and 5 which are mentioned in Chart I showed more evidence of inflammatory brain disease. In these cases leukocytes and lymphocytes were found in the perivascular space and in the leptomeninges plasma cells were also present. This seems to indicate that the condition was either complicated by encephalitis which had developed sometime before death, or encephalitis may have been a major factor. A similar picture, as seen in Cases 3, 4 and 5, has been described

by H. H. Noran (22), and Noran considers the pathology as so typical of equine encephalitis that he thinks the diagnosis may be made without further epidemiological evidence. The pathology is also similar in some points to that found in toxoplasmic encephalomyelitis which has been thoroughly studied by Abner Wolf (23) and co-workers in recent years.

In some doubtful cases the pathologists will, therefore, not be able to determine the share which trauma or encephalitis played in the production of this type of pathology. There is, however, evidence that mantle sclerosis can occur without encephalitis due to trauma and occlusion of the superior sagittal sinus.

Group II. Cystic Degeneration of the Brain

This condition has been described under the names of central porencephaly (Schwartz), encephaloclastic porencephaly (Jakovlev (9)), false porencephaly and central encephalomalacia.

CHART 2
Cystic degeneration
(Pathology: Group 2)

CASE NUMBER	MENTAL STATUS AND SEX	AGE AT DEATH	BIRTH	EPILEPTIC SEIZURES	CLINICAL SYMPTOMS
6 (37/3)	Idiot F	3 yrs.	Full term. 7½ lbs.	Generalized clonic, tonic fits at 9 months.	Spastic paraplegia of arms and legs. Grasping position of right hand. Microcephaly (17½").
7 (33/18)	Idiot F	2	Prolonged labor. Prolapsed cord. Asphyxia. Little breathing for 3 hrs. Forceps delivery.	Grand mal and petit mal at least after age of 6 months. In last year, daily.	Slight spasticity of arms and legs 1st wk. after birth. High pitched crying. Feeding problem. Contracted pupils. Hemorrhages into eyeballs. Nystagmus and progressive decerebrate rigidity. Microcephaly (14½").
8 (41/76)	Idiot M	4	Instrumental. 5-½ lbs.	At one month frequent convulsions for several wks. Breathing difficult with periods of cyanosis.	Progressive paraplegia of arms and legs with progressive decerebrate rigidity.

The condition is characterized by the formation of cystic cavities in the central white matter (Plate 2). The cortex and the white cores of the convolutions are primarily not involved. The cysts are formed outside of the basal ganglia and in the beginning are not in communication with the ventricular system. Only after large parts of the central white matter have been destroyed may they break through to the ventricular system. Then some cavities appear in communication with the ventricles. The cysts vary greatly in size and are filled with a meshwork if they are small. In larger cysts, however, the cavity shows only few fiber strands and the cavity is filled with a clear fluid. The cavity wall contains numerous glia cells but the glia wall is not very strong and is likely to break down gradually. In this way progressively larger cavities are formed and a whole lobe may be destroyed, leaving a cyst covered by greatly thickened leptomeningeal membranes. In this stage the cortical architecture is destroyed, but remnants of gray matter may still be recognizable.

This type of lesion is not related to any particular vascular patterns, but seems to depend upon ischemic necrosis. It is still a matter of argument whether long lasting asphyxiation at birth alone can produce the ischemic necrosis of the white matter. The histories of some cases suggest asphyxiation as a factor of main importance. Some authors feel that crushing of brain tissue is to be postulated as an additional factor. The condition is one of early infancy and it is not found in older children after the brain has matured and myelination of the white matter is far advanced. In older children only small, single cysts may develop after injuries of various kinds. On the other hand, cystic degeneration is not found in still-born babies or new-born infants who die from a birth injury immediately after birth. The earliest time when cystic cavities may be discovered seems to be four weeks after birth. This indicates clearly a relationship between this condition and birth pathology.

Spatz (21) has suggested that the cavities are due to the fact that the infant's brain is not able to produce a sufficient glia reaction. A microscopic study of the brains, however, suggests that the inability of the glia to react may be due to the extent of damage in which all tissue elements are involved to the same extent. It seems to me a simpler explanation to assume that the amount of damage and the suddenness of the onset in the traumatic lesions leads to a complete destruction of all tissue elements with resulting edema and accumulation of fluid. If parts are less damaged they show glia reactions and the walls of smaller cavities are frequently formed by glia tissue.

Although we have seen that in the first group small sub-cortical cysts are found, the "cystic degeneration of the brain" (encephaloclastic porencephaly) represents a separate pathological entity, the lesions of this group being quite different from those of the first group, as described.

Cystic degeneration is represented by three cases which are summarized in Chart 2. These three cases show different stages of the same condition and it seems as if the three children who died at an age of two years, three years, and four years, respectively, show the different stages of the same process according to the length of time of progress. Case seven showed numerous small cavities with confluence of smaller holes, but in no place had the cavities assumed the size of a whole lobe. The cysts were placed mainly beneath the insular cortex and in the centrum semiovale. The lateral ventricles were somewhat enlarged. The cortical architecture was little involved.

In case six the cavities which were placed in exactly the same position had developed to large holes which had destroyed the cortex and filled large parts of the temporal lobe and smaller parts of the frontal lobes. The process was present on both sides but to a different extent. The cavities showed a meshwork of fibrous trabeculae which crossed them and they were filled with a clear fluid. The brain did not appear collapsed when viewed from the outside at autopsy, but collapse of the cavities occurred as soon as the wall was opened.

The eighth case which seemed to be the most advanced showed complete destruction of both hemispheres. The basal ganglia were covered by membranes which contained only small amounts of brain tissue. The ventricles were enlarged and the walls between ventricles and cysts completely destroyed. Between the leptomeninges and the dura there was also a large space filled with fluid.

Group III. Diffuse Patchy Devastation

This condition has not yet been described as an entity resulting from birth injuries. The condition is characterized by diffuse patchy devastation of the cortical layers, vasoparetic cortical congestion, leptomeningeal fibrosis, brain atrophy with enlargement of the lateral ventricles and areas of central necrosis and demyelination. The condition is frequently associated with a *status marmoratus* found in parts of the basal ganglia and even in parts of the cortex.

The cortical lesions were often associated with small areas of necrosis and cystic degeneration near the ventricle walls. The localization of these areas of necrosis is related to the venous system about the basal ganglia. Holland (4)

and Schwartz (5) have demonstrated a connection between these lesions and the drainage of the brain into the great vein of Galen. The particular course of this vein renders it vulnerable to stasis, retrograde congestion and tearing with resulting multiple hemorrhages in the region of the tributaries of the terminal cerebral veins, especially the terminal veins and the veins along the thalamus and caudate nucleus. The hemorrhages lead to sub-ependymal necrosis with consequent enlargement of the lateral ventricles and atrophy of the basal ganglia.

The case of a patient (#15), Chart 3, who reached an age of 23 years may be most suitable to describe the pathological findings in this group. The patient developed convulsions at the age of 5 weeks. The girl did not learn to walk before the age of 7 years. She could feed herself but did not talk. Her gait was always unsteady and hesitant. At 13, she again developed epileptic seizures and crying spells which were regarded as epileptic equivalents. She died in an epileptic status.

A series of coronal sections through the brain (Plate 4) revealed at the level of the anterior commissure that the ventricles were asymmetrically enlarged. The right caudate nucleus was much smaller than the left and the sub-ependymal tissue was necrotic along the ventricle wall. The tissue showed small cysts divided by a fine mesh work; the terminal vein and smaller tributary vessels were greatly enlarged and suspended in the meshwork. The capsula interna was interrupted and partly blotted out. On the other side there was sub-ependymal necrosis with stasis of the terminal vein but to a less extent. Another section at the level of the columns of the fornix showed extensive sub-ependymal necrosis on both sides with interruption of the internal capsule at its ventral end. In another section through the mammillary bodies, a rather large sub-ependymal cyst was found beneath the wall of the left lateral ventricle and above the third ventricle.

These observations demonstrate clearly that the lesion in this case was due to ischemic hemorrhagic necrosis similar to that seen in the previous group, but more diffuse in character and less extensive. From the observation of the basal ganglia the cortical lesions were more easily understood. There was extreme congestion with dilatation of the capillaries and stasis in the larger vessels. The cortex showed innumerable small areas of devastation and necrosis. The white matter showed spots of hypermyelination. (Plaques myeliniques)

Sixteen similar cases are recorded in Chart 3.

With the exception of four cases, in which the birth history was non-contributory, cases had a rather uniform story with only slight variations. Such a history is given in the following case (#22). Both parents of the child were young and healthy people. The patient was a first child, and there were two smaller siblings, both normal; no miscarriages or stillbirths. Our patient was born at full term by instrumental delivery after long labor. It was cyanotic and said to have been comatose for a whole week. A series of convulsions was observed in the first 24 hours. The child was a difficult feeding problem for a whole month, and she did not cry or make any noises for two months. During that time was not expected to live, but she improved gradually. When, however, the time came for her to sit up, move around, and start to talk, it was observed that she did not make an attempt of that sort or take notice of her surroundings. Her muscles were flabby, and she was listless. A pneumo-encephalogram made at an age of 2 years showed bilateral enlarged ventricles, and considerable amount of air above the convexity. She never learned to walk; she was an attractive, nice-looking little girl, who needed the care of a sanatorium. At an age of 4 years, she suddenly developed *status epilepticus* and died without recovering from that state.

The convolitional patterns appeared normal, but the convolutions were slightly flattened through pressure and the sulci, even the Sylvian fissures were closed through pressure. Some fibrotic and gliotic bridging between adjacent convolutions. An epidural organized blood clot was found in the occipital region. The lateral ventricles appeared slightly

larged. The *corpus callosum* was thin and the white matter as a whole not well myelinated. There was the same type of diffuse patchy degeneration, spread all over the cortex which was described in case 15.

CHART 3
Patchy cortical devastation
(Pathology: Group 3)

CASE NUMBER	MENTAL STATUS AND SEX	AGE AT DEATH	BIRTH	EPILEPTIC SEIZURES	CLINICAL SYMPTOMS
9 (37/4)	Imbec. M	375. 15	Full term? Long hard labor. 3½ pounds.	None	Right Hemiplegia. Hypotonia. Bulbar paralysis. Unsteady gait.
10 (37/5)	Idiot M	21½	Full term. Prolonged. Instrumental.	Periods of stertorous breathing. Died in epilepticstatus.	Stiffening of muscles. Bleeding from nose and mouth after birth. Mobilespasticity of legs. Never walked. High pitched, shrill crying.
11 (37/9)	Idiot F	7½	Full term "Blue baby."	After birth attacks of cyanosis with stiffening of whole body, vomiting, and high pitched crying. Later epilepsy.	Clumsy gait. Hyperactiveresflexes. Purposeless motions of arms and hands.
12 (38/16)	Idiot F	6	Caesarian section. Asphyxiation. Resuscitation with difficulty. 5lbs. 6 ozs.	Epileptic seizures at irregular intervals.	Little crying first three months. Never walked or talked. Tremor of head. Peculiar arm movements. Anisocoria. X-ray showed enlarged ventricles and excessive air.
13 (38/19)	Idiot F	16	Caesarian section	Up to 32 fits per month, since age of seven years.	Strabismus. Unable to hold up head. No speech or gait. Hyperactive reflexes; purposeless movements.
14 (38/21)	Idiot M	3	High forceps. Prominent caput succedaneum. Resuscitated with difficulty. 6½ lbs.	Difficulties in swallowing at six months. Spells of vomiting.	Infantile spastic paralysis of legs. Hands atonic. Motions atactic.
15 (38/30)	Idiot F	23	"Normal"	Convulsions at 5 weeks, again at 2 yrs., and since age of 13 yrs. Died in status epilepticus.	Slow development. Internal strabismus. Anisocoria. Never talked. Unsteady gait.
16 (40/52)	Idiot F	12	Premature. Induced by bagging on account of high blood pressure.	At age of 6, convulsions, and again at irregular intervals since age of 11.	Asymmetrical facies. Hyperactive reflexes. Awkward gait, walking on her toes. Shaking of wrists.
17 (46/78)	Imbec. F	3	"Normal" 6½ lbs.	Sudden death with cyanosis	Retardation. Listless. Unable to sit up. Alternating internal strabismus. Sluggish light reaction. Anisocoria. Hyperactive reflexes. Head circ. 18½

CHART 3—Continued

CASE NUMBER	MENTAL STATUS AND SEX	AGE AT DEATH	BIRTH	EPILEPTIC SEIZURES	CLINICAL SYMPTOMS
18 (42/88)	Idiot M	7 $\frac{1}{2}$ 19	Full term rapid labor lasting 1 hr.	Convulsions 1st yr. of life.	Difficulties in nursing. Listless. Slow. Nystagmus. "Cataracts" of both eyes. Unsteady gait.
19 (42/93)	Idiot F	12	Full term instrumental, high forceps. 18 hrs. labor. Lacerations of face and forehead, depressed skull.	None	Slow development in first year. Listless. Unable to sit up. Never walked or talked. Soiled bed and clothing. Flabby, atrophic arms. Valgus position of feet. Mobile spasm of legs.
20 (43/101)	Moron M	54	Premature, after accident to mother. Face presentation. Forceps delivery. Skull deformed.	None	Retardation. Restless. Distractible. Behavior problem. Skull indentation and defect in childhood. Operated by nerve surgeon.
21 (43/104)	Idiot M	29 $\frac{1}{2}$	Normal, full term.	Several convulsions in early life.	No talk, destructive idiot, Head well formed (22 $\frac{1}{2}$) excentric pupils.
22 (43/108)	Idiot F	4 $\frac{1}{2}$	Full term, long labor, instrumental.	Cyanotic and comatous for week. Convulsions for 24 hrs. after birth. Feeding problem, difficulties in swallowing.	Feeding problem 1 month, no noises for 2 months. Never walked or talked, motionless, flaccid. Strabismus, optic atrophy. Head asymmetrical (18 $\frac{1}{2}$). Mobile spasm.
23 (43/113)	Idiot	13 $\frac{1}{2}$	Full term, instrumental, "considerable trauma to head with molding, face and head badly cut."	Not reported. Knocked head against crib and floor. Attacks of screaming and abnormal breathing.	Feeding problem. No walk or talk before 5. Learned walking after 5. Strabismus. No speech. Tics of head, tremulous motions of hands. Head circumference normal.
24 (43/117)	Imbec. M	32 $\frac{1}{2}$	Difficult birth, breech presentation instrumental.	Frequent fainting spells with loss of consciousness for $\frac{1}{2}$ hour. Slow breathing, stopping of heart sounds.	Facial asymmetry, strabismus. Head circ. 19.5", queer shaped. Ptosis.

IV. ETIOLOGICAL FACTORS

Since the syndrome of birth injury accounts for 30% to 40% of the severe cases of mental deficiency occurring in families who could ordinarily expect normal offspring, it is imperative that the physicians acquaint themselves thoroughly with the pathological and clinical features.

A consideration of the modes of birth most apt to cause injury indicated that every type was represented in the case material. The following list shows the incidence of the various types of births among the cases.

	Cases
Prematurity.....	4
Breech presentation.....	2
Prolonged labor.....	5
Full term rapid labor.....	1
High forceps.....	5
Caesarian section.....	2
Normal without comment.....	4
Full term blue baby.....	1
One of twins.....	2
	<hr/> 26

Twenty six different modes were observed in twenty four cases due to the fact that in some cases two factors were present simultaneously.

One case of breech presentation was one of twins.

In the first case of prolonged labor (7) the child had a prolapsed cord and asphyxiation. As a result, the birth had to be forced and accomplished hurriedly by forceps. It took several hours to resuscitate the asphyxiated child. The second child with long hard labor was born with a birth weight of $3\frac{1}{2}$ pounds. The third case manifested severe difficulties at birth and was born with a prominent *caput succedaneum*. This patient was resuscitated only with great difficulty. The fourth child was delivered by high forceps after eighteen hours of unsuccessful labor. She had lacerations of the face and forehead, and a depressed skull.

In one of the cases of Caesarian section the operation had been performed only after many hours of unsuccessful labor, and the child was born asphyxiated; there was considerable difficulty in resuscitation. In the second case of Caesarian section no information was available. Clifford (11), in his study on "The Effects of Asphyxia on the New-born Infant," has pointed out that Caesarian section is performed in order to save a child who is asphyxiated even before entering the birth canal. His study included eleven new-born infants. All had been delivered by Caesarian section because of fetal anoxemia produced by the separation of the low-attached placenta previa accompanied by active hemorrhage just prior to birth. It is therefore not the operation which is a specific danger to the child, but the condition in which the child is previous to delivery.

As long as birth injuries were considered the result of mechanical injuries, their cause was sought in the administration of forceps, and the possibility of an injury in the course of a natural birth without forceps was barely considered. It has, however, been increasingly recognized that the use of a forceps in itself rarely causes a birth injury, except if a high forceps had to be used under adverse conditions. The efforts of many investigators have collected evidence as to the various etiological factors which may briefly be surveyed in the following.

Prematurity

There is an accumulation of evidence to show that prematurity is one of the main factors in neonatal death. A definite relationship has been established

between the weight of the newborn and the percentage of intracranial hemorrhages found as the cause of neonatal deaths. Arvin Ylppoe (7) has made such a correlation chart which is seen below. Of those children with a birth weight of less than three pounds who died of unknown causes, 90% showed the presence of cerebral hemorrhages. In the group of premature babies with a birth weight below four pounds, intracranial hemorrhages were found as the cause of death in 76%. The percentage decreases proportionally with increase in birth weight.

In a recent paper by S. Z. Levine and H. A. Gordon (12), "Physiologic Handicaps of the Premature Infant" a very clear summary is given concerning the condition of the premature child. These authors quote the figures prepared by the Children's Bureau on neonatal mortality in the United States, which showed that prematurity contributed with 47% to neonatal deaths, representing the greatest single item among the various causes. Injury at birth follows second with 14%.

Premature birth constitutes a danger to the child for two reasons. The organism of the mother is not yet ready for the birth act. As a consequence, lack of elasticity of the tissue and its inability to yield to the passage of the

CHART 4

Relationship between birth weights and frequency of intracranial hemorrhages in premature babies according to A. Ylppoe

BIRTH WEIGHT	NUMBER OF CASES	HEMORRHAGES	PERCENTAGE
Below 1000 gr.	20	18	90
1001-1500 gr.	51	39	76.5
1501-2000 gr.	17	6	35.3
2001-2500 gr.	15	4	26.7

child increase the pressure upon the child to a considerable degree. In addition, the child himself is far less prepared to resist increased pressure than is a full term baby. The ossification of the skull is less advanced; the brain tissue is softer and less myelinated; the nerve centers are less mature; and the response to stimuli is diminished. The blood vessels are immature and far less able to resist congestion and increased pressure. Slight degrees of tearing will lead to rupture of the vessels and increased bleeding, a condition which is aggravated through the fact that the blood has less capacity to coagulate. Hemorrhages and asphyxiation not only occur more easily in the premature child, but he is less well-prepared to cope with any adverse condition, and both of these factors reduce his prospects for life and health. As the main handicaps of the premature baby, Levine and Gordon offer Chart 5.¹

Abnormal positions

As second cause of birth injury, abnormal positions of the child should be recognized. It has been known for a long time that a transverse position which

¹ Amer. Jour. Dis. Child., Vol. 61, p. 275, August, 1912.

demands version is dangerous. But the fact that breech presentation is also extremely hazardous to the child has been realized to a lesser extent. In breech presentation the blood is squeezed from the body towards the head so that the head enters the birth canal in an extremely congested condition while under normal conditions the blood is squeezed out of the brain into the body. It is clear that the tightly filled vessels of the head in breech presentation readily produce rupture of the vessels with ensuing hemorrhages. The vessels suffer extreme enlargement, sometimes beyond the limits of contractility, and the relaxed hyperemic vessels are unable to regain their tone immediately after birth. The presence of long-lasting stasis with its malnutrition of brain tissue causes multiple necrosis and perivascular softening. This condition is aggra-

CHART 5

Handicaps of the premature infant

PHYSIOLOGIC MANIFESTATIONS	PATHOLOGIC EXAGGERATIONS
1. Difficulties of respiration	Asphyxial attacks, aspiration pneumonia
2. Difficulties of circulation	Cyanosis of extremities, edema
3. Faulty control of body temperature	Hypothermia and hyperthermia
4. Diminished alimentary tolerance	Gastrointestinal upsets
5. Increased capillary fragility	Hemorrhage
6. Impairment of renal function	Dehydration and acidosis
7. Inadequate antenatal storage	Rickets, scurvy, anemia
	Infections
Minerals and vitamins	
Immune substances	
8. Defective hemopoiesis	Anemia
9. Hepatic immaturity	
Bilirubinemia	Jaundice
Hypoglycemia	Shock
Hypoproteinemia	Edema
Hypoprothrombinemia	Hemorrhage
10. Increased content of body water	Infections, edema
11. Incomplete development of enzyme systems	Absence of creatinuria, faulty metabolism of aromatic amino acids, impaired formation of hemoglobin

vated by the fact that the umbilical cord is frequently compressed between head and pelvis for the whole period in which the head has to pass the birth canal. If the birth is slow, the compression of the cord may last for a considerable time, during which the circulation of the brain is virtually stopped. Obstetricians have learned to watch the heart beats of the child and to accelerate birth as soon as the heart is imperiled, but as long as the heart pulsation is maintained at all, and birth seems to progress in a satisfactory manner, the malnutrition of the brain is considered a factor of secondary importance. Recent experiments, however, have provided evidence that an interruption of circulation as short as three minutes and twenty five seconds may suffice to damage nerve tissue beyond repair. Although the new born brain may be more resistant to

asphyxiation, it is not surprising to find that breech presentation may produce damage in spite of the fact that children born by breech presentation frequently show very little malformation of the head and are born in better condition than children with the head first.

A last factor in cases of breech presentation is the fact that the exposure of the body to the air may stimulate the beginning of breathing before the head is completely delivered. Aspiration of foreign material causes many neonatal pneumonias, which represent a grave danger.

Long-lasting birth

The dangers of a long-lasting birth are represented in the fact that after rupture of the bag the head of the child is pressed against the pelvis and cervical ring, while the pressure upon the body of the child is a different one. Schwartz (5) has put special emphasis upon the pressure difference and has attributed a great number of cerebral injuries at birth to "low pressure-suction." He goes so far as to find some relationship between the point of intracerebral hemorrhage and the part of the head which advances first.

The intrauterine pressure exercised by the contraction of the uterus is, according to Schwartz, 10 to 15 mm. Hg before the water bag ruptures. During the period of expulsion the contractions of the uterus and of the abdominal musculature represent a pressure of 80 mm. Hg, but in some births the pressure which is exercised upon the body of the child and the pressure to which the head is exposed at the entrance to the birth canal is equal to the weight of twenty-four kilograms (53 pounds). He also attributes great importance to the pulling effect of suction during the birth action, which increases the deformity of the fetal skull. The *caput succedaneum* is thought by Schwartz to be due to the pressure difference; venous intracranial hemorrhages beneath the birth "tumor" are frequent.

Although Schwartz has put great emphasis upon the suction theory, it has not been generally accepted, and it certainly represents only one factor within a more complex chain of events. Rydberg (13) points out that there is a high incidence of bleedings into the brain substance, meninges, and ventricles, but that "as a rule the most minute investigation does not reveal the source of the bleeding. They appear to be multiple in origin, and everything indicates that they are due to a more generalized vascular strain and not merely to an impediment in the venous efflux of limited vascular regions." (p. 93). He refers to Cushing's experiments and says "that it is possible to produce vascular lesions and bleedings if the intracranial pressure is brought up to a high level and then rapidly reduced. The animals then succumb, showing the usual symptoms of paralysis,—decreased blood pressure, accompanied by rapid and small pulse; and autopsy shows the brain substance to be dotted with capillary bleeding." Rydberg, applying the results obtained from experimental physiology to the fetus, thinks that the compression of the head, when the head is engaged, is followed by "increasing intracranial pressure, which brings about a rise in the blood pressure." Consequently the cranial compression does not cause any

mechanical strain upon the vessels; the equilibrium between intravascular and extravascular pressure is only disturbed if there occurs a sudden fall in the intracranial pressure. This may happen at the moment of the cessation of a pain if the fetal blood pressure is raised to a high level.

A stronger effect of the same sort results on sudden changes in the elastic counter-pressure of the walls in the birth channel when the head rapidly passes from a narrow to a wide part. Such a situation is encountered, for instance, in the case of a contracted pelvis and violent pains, when the head, as it sometimes does, moves very rapidly down into the pelvic cavity after a maximum of compression in the pelvic inlet.

In breech deliveries the still unmodelled head is sometimes drawn violently through the pelvis. In such cases a very abrupt compression of the head takes place, immediately followed by a relaxation of the external pressure.

"Cases of that kind are obviously most liable to injuries due to rapid fluctuations in the intracranial pressure, and are also subject to over-stretching of the cranial supportive apparatus. And it is in such cases, too, that tentorial tears and bleedings are very common" (p. 94).

Rapid birth

That even very precipitate birth may involve great danger has been recognized increasingly during the last few years, and has been explained by the effect of sudden pressure changes of the same type as seen in deep sea diving. The sudden decrease of pressure upon the skull of the child after rapid birth seems to produce readily tearing of the subdural blood spaces and leads to slowly progressive venous hemorrhages, which may develop on the second day after birth. The condition of the child after Caesarian section is more complicated, but some of the hemorrhages encountered in babies born in this manner seem to depend on the same factors as those in precipitate birth. Other factors, such as immaturity, and narcotics, also come into play.

Asphyxiation

The role of asphyxiation has been the subject of many arguments. In earlier years, asphyxiation was considered of major importance and obstetricians felt compelled to avoid any asphyxiation, for instance in breech presentation, and to produce a baby by instruments under the risk that the forced delivery may cause mechanical damage. When it was discovered that the majority of babies who died with the diagnosis "asphyxiation" had some kind of extra or intracerebral hemorrhages, the role of asphyxiation as a danger factor was almost completely denied (Ehrenfest (14)). Recently, however, increased knowledge of anoxia has again centered interest upon the various types of anoxic, anemic, stagnant and histotoxic anoxia.

Since the classical presentation of the "Survival Time of Different Nerve Tissues" by Cannon and Busket (15) (1913), it has been generally accepted that damage to the nerve cells of the cerebral cortex may occur and be permanent in spite of the fact that the medullary centers may still function. Experi-

LATE EFFECTS OF CEREBRAL BIRTH INJURIES

mental work on the influence of anoxic and histotoxic anoxia has accrued evidence beyond argument, that anoxia is one of the most important for diffuse cerebral cell death and destruction. Application of these observations to the problem of birth injury has been suggested by writers. Schreiber (16) especially has emphasized the role of narcotic to the mother during delivery. For the student of the late effects of injuries, it is impossible to estimate the role of hemorrhages or mere anoxia since the latter produces stasis and subsequent anemic or hemorrhagic infarction. It is sufficient to mention that many observations on late effects of birth injuries are well in line with recent experimental observations and some phenomena are more easily understood if asphyxiation is considered as one of the contributory agents.

Mechanical injuries

We have seen that numerous reasons account for the occurrence of birth injuries without the use of forceps. It is therefore well understood that mechanical injuries do not retain first place among the possible causes for damage at birth. But, if a forceps had to be used under difficult conditions and the head has suffered a considerable malformation and compression, injuries encountered under these conditions are of especially severe type. Otto Marburg (17) reported 455 newborn children who died, 80 cases of laceration of the tentorium, 68 cases of tearing with subdural hemorrhage, 3 cases of hemorrhage into the cerebellum, and 12 cases without noticeable hemorrhage.

The mechanism of tears of the tentorium and the falx is well understood from the observations of Beneke (18) and Holland (4). Tears of the falx and tentorium are frequent. They produce ruptures of the sinuses or of the veins, or, in rarer cases, arteries. The various localizations of epidural or subarachnoid hemorrhages depend on the localization of the tear. It depends on the type of presentation of the child's head. As a result, epidural hemorrhages upon the convexity of the brain are found in damage of the falx and tentorium, while tentorial tears are the most frequent causes of subdural hemorrhages around the cerebellum, pons and medulla. Tears on the border of the tentorium, which indicate the great stress under which the child has been born, result in two types of lesions: damage to branches of the middle cerebral artery, and damage to the straight sinus and the vena magna. Interruption of the drainage of blood from central parts of the brain in the venous sinus system. It is beyond the limits of this discussion to deal in detail with the varying types of mechanical injuries. It suffices to emphasize that mechanical injuries are of great importance, and that with improved medical treatment many children now survive severe brain injury but are not well enough to be discharged without encountered injury without surgical interference.

of a birth injury after any mode of birth. If we now consider the relationship between the pathological findings and the clinical manifestations, a closer correlation may be observed.

Amongst many clinical aspects, two seem to be of special interest. The first question is whether a child is likely to manifest signs of an unrecognized birth injury in later life, in spite of the fact that a damage was not suspected at birth. The material presented seems to indicate that most of the birth injuries seem to produce immediate symptoms which suggest the occurrence of brain damage.

Our material reveals retrospectively that in spite of incomplete information, 13 cases or 54 per cent displayed signs of brain damage immediately after birth. Severe asphyxiation, external lacerations, circulatory deficiency or intracranial hemorrhages were present and might account for the pathological findings. In 10 cases or 42 per cent, the morbid condition made itself manifest a few weeks, or at least months, after birth, and in only one case was the abnormal condition not mentioned before the second year of life. A careful examination in this case would certainly have revealed the brain damage much earlier. We may conclude, therefore, that brain damage as a consequence of a birth injury manifests itself either at birth or not later than in the first six to nine

CHART 6

BIRTH INJURY ESTABLISHED	GROUP 1	GROUP 2	GROUP 3
Immediately after birth.....	3	1	9
In first six months.....	1	2	7
After first year.....	1		.

months of life. If a child has been perfectly normal during that period, it may be concluded that such a child will not suffer from late effects of a birth injury. If, on the other hand, a child reveals signs of a brain damage after birth the prognosis is not good. This observation is in accord with the observations of Erik Rydberg (13), who found that 33 per cent of children with major brain injury later in life became idiots or imbeciles. Of forty eight cases which he followed only eight or nine exhibited fully normal conditions after a period ranging from two to eighteen years. It may be mentioned that if a bloody spinal fluid is encountered after birth as the only finding in an otherwise normal child it cannot be considered as evidence of brain damage and is so common that it should be discarded as of no significance.

The study of autopsied cases offers an opportunity to collect data which are of interest for the diagnosis of birth injury and for the differential diagnosis between a birth injury and a developmental disorder of the prenatal period. The latter differential diagnosis is of importance from many points of view. The presence of a mentally deficient child represents a heavy tax upon the other members of the family because of the general feeling that mental deficiency is in some way a sign of inferior heredity and therefore some taint. The pediatrician who acts in an advisory role to a family will be frequently asked

for his advice with regard to further offspring and the future chances of other members of the family. If the one mentally deficient child is the result of a birth injury, the physician will certainly not hesitate to comfort the family and encourage the parents to have more offspring. If, on the other hand, the child reveals developmental disorders, a much more careful consideration of all pertinent factors is necessary to predict the future of other siblings. Furthermore, the patient himself should be treated and managed in a different way if his condition is the result of a brain injury than if it is due to abnormal development. Although the general medical attitude toward the management of a birth-injured child is still conservative and that of waiting, I believe that this attitude will change and will be replaced by more active measures. The poor prognosis of these children would justify the taking of greater risks.

With regard to the differential diagnosis between prenatal developmental disorders and birth injuries, a careful collection of data will enable the physician to establish such a diagnosis with a great amount of accuracy. Developmental disorders of the nervous system are likely to display other signs of faulty development. True microcephaly is recognized at birth because in this condition the skull has failed to reach, at the end of the gestation period, the normal circumference of 34 cm. or 13½ in. The abnormal outline of the microcephalic skull indicates the prenatal pathology. A circumference of less than 31 cm. is also diagnostic of microcephaly. Measurements of the length of the skull in the new born (normal 11.5 to 12 cm.) and the width (normal 9.5 cm.) will also help in the diagnosis. Congenital malformations of the nervous system are frequently associated with cleft formations, meningocele, myelomeningocele or *spina bifida occulta*, cleft formation in the cerebellum or abnormal skull ossification. Even remote developmental disorders like cleft palate, hare lip, webbed fingers or toes, undescended testicles and congenital subluxations or bone anomalies, suggest the existence of factors active during the prenatal period and are in favor of a prenatal disorder rather than an uncomplicated birth injury. The following chart (Chart 7) summarizes some observations with regard to children seen at an older age.

As far as the diagnosis of a birth injury is concerned an analysis of the material indicates the following:

Only in five of the twenty-four cases was the birth considered "normal" without further comment. One of the full term babies was recognized as a "blue baby" at birth. In this case, attacks of cyanosis with stiffening of the whole body, vomiting, and high-pitched crying were recognized shortly after birth and indicated a severe intracranial accident (#11). One of the "normal" born children (#3) had seizures two days after birth and continued to have periods of stiffening and crying for ten days. The diagnosis of an intercerebral hemorrhage was made by a physician at that time. Case #7 revealed slight spasticity of arms and legs in the first week after birth, high-pitched crying, contracted pupils, and feeding problems. Case #10 had stertorous breathing spells and stiffening of the muscles, in addition to bleeding from the nose and mouth after birth. Case #12 showed general hypotonia and cried very little

in the first three months. Case #9 had a right hemiplegia and hypotonia. Case #6 showed spasms and tremors. Two cases, #7 and #18, had severe hemorrhages into both eyeballs. In Case #7 these hemorrhages were recognized as such but in Case #18 they were noticed a few weeks after birth and mistaken for congenital cataracts. The autopsy established the hemorrhagic character of these "cataracts" beyond doubt. Case #22 was cyanotic and "comatose" for a whole week after birth and had a series of convulsions for the first 24 hours.

CHART 7

Differential diagnosis between birth injury cases and developmental mental deficiency

	BIRTH INJURY	"UNDIFFERENTIATED" MENTAL DEFICIENCY
Family history	Other members of family normal.	Mental deficiency or illness frequent in other members of family.
Physical examination	Child well-formed. Fine skin. Hair normal. No malformations of body organs. No "stigmata."	Physical stigmata. Skin anomalies. Cleft formations in spine, palate. Bony dysplasias. Gonadal anomalies.
Skull	Asymmetric, depressed or bulging. Frequently "normal."	Symmetrical. Brachycephalic, dolicocephalic, or rounded and small.
Microcephaly	Circumference usually 17-19". Never less than 15". Frequently more than 20"	True microcephaly (below 14) or circumference of about 20"
Motor activity	Paraplegias most frequent. Hemiplegias. Decerebrate rigidity in cystic degeneration. Mobile spasms and hypotonia in asphyxiation or hemorrhages of terminal veins.	General awkwardness. Localized neurological signs rare.
Eyes	Anisocoria. Nystagmus. Strabismus.	Symmetrical pupils. No nystagmus. Strabismus frequent.
Epileptic seizures	In at least 80% occasional convulsions. Seizures after birth especially significant.	May be present several years after birth. Rare in first years of life.
Psychological classification	Idiocy or low grade imbecility most frequent. High grade imbecility rare. Occasionally morons with some neurological symptoms.	Imbecility frequent. Idiocy only if associated with congenital malformation of brain.

Some of the symptoms which resulted from a birth injury are listed in Chart 8. A factor of great interest seems to be the frequency of epileptic convulsions. All three patients of group 2 were reported to have had convulsions. In Group 1, four of the five patients were reported to have had convulsions and in the last group, nine out of sixteen cases had definite convulsive seizures. This term does not include fainting spells with loss of consciousness which were observed in the last patient, attacks of screaming and abnormal breathing which were seen in Case # 23, and spells of cyanosis in one of which the patient finally died, which were seen in Case #17. Case #11 also revealed attacks of cyanosis

with stiffening of the whole body, vomiting, and high-pitched crying. Case #14 revealed attacks of difficulties in swallowing. This brings the number of patients who suffered from "pathological spells" up to 20 out of 24 patients. The early onset of these spells is of great value for the diagnosis of a birth injury. Wilder Penfield and Erickson (19) mention the same experience and emphasize that epileptic seizures in early infancy are suggestive of a birth injury.

Beside epileptic seizures, there were a number of neurological conditions which deserve interest. As a matter of fact, not a single child was without some neurological disorder and it should be generally accepted that the birth-injured child is a patient with brain damage in which the mental deficiency is but one symptom among several others which are equally important. It seems hardly justified, as is usually done, to classify the birth-injured imbecile or idiot among

CHART 8
Symptomatology in birth-injured children

SYMPTOMS	PATHOLOGY GROUPS		
	1	2	3
Epileptic Seizures	4	3	9
Attacks of cyanosis and pathol. breathing			4
Spastic paraplegia of legs	4	3	4
Hemiplegia	1		1
Mobile Spasm of arms and legs			3
Unsteady gait			7
Athetoid-choreatic movements			4
Head circumference below 16 ins.		1	
16-17 ins.		1	
17-18 "	2	1	
18-19 "	1		3
19-20 "	2		1
above 20 ins.			12
Idiocy	4	3	12
Imbecility	1		3
Moron			1

the general group of feeble-mindedness. They are post-traumatic patients who need special attention and treatment.

As the chart indicates, spastic paraplegia of the legs was found in group one 4 times, in group two 3 times and in group three 4 times. Although the lesions in the three groups varied greatly, spastic paraplegia was found associated with all three types of alteration. If the name of infantile cerebral spastic paralysis (Freud) is synonymous with "Little's Disease," this condition was present eleven times or in 46%. Although the lesions were more marked in one hemisphere in the first group and some of the cases showed hemi-atrophy, the paraplegia affected both sides almost equally. The explanation is that the micro-copic study revealed lesions in both hemispheres although in somewhat different degree. All three cases of the second group eventually developed quadriplegia with great stiffness and rigidity, it being characteristic that the

condition was progressive. Although at a single neurological examination it would be difficult to distinguish this group from "Little's Disease," which is stationary and may even show some improvement, these cases were cases of progressive decerebrate rigidity and should be differentiated from cases of "Little's Disease." Four cases of the third group revealed the typical picture described by Little in spite of the fact that gross lesions in the brain were not recognizable and only the microscopic examination demonstrated the condition. In none of these cases was the morbid process restricted to the basal ganglia.

Hemiplegia was present in one case of group one with hemi-atrophy of the brain and in one case of group three with very diffuse lesions in the cortex and even in the spinal cord.

A symptom somewhat characteristic of the third group is "mobile spasm" with inability to walk. These children were bedridden at first with a condition of flabbiness and spasticity. Spasticity to a minor degree was present in seven additional cases. The children learned to walk at a late date (mostly after five years), and were finally able to move around but the gait remained unsteady and awkward. With seven cases of unsteady gait, three mobile spasm, one hemiplegia and four true paraplegias, only one patient of the third group is left without evidence of motor disability. Four patients showed purposeless movements of the arms which may be classified as "athetoid-choreatic" movements.

Head measurements are of interest because they also indicate the presence of a morbid process. The lowest measurements were found in the second group in which all children were definitely microcephalic. The cystic degeneration (encephaloclastic porencephaly) which was found in these cases apparently develops rapidly after the birth trauma and seems to be associated with a complete arrest of brain growth after the onset of the pathology. The condition seems, however, to be definitely of a post-natal character, since cystic degeneration has not been reported in newborn or stillborn babies, in spite of the huge autopsy material which has been collected of cases of neo-natal deaths in many different places. Last year Stevenson (20) reported seven cases of cystic degeneration in babies, the youngest of which was one month old. The cases do not represent a uniform group. In three of his cases, the cystic degeneration was the result of syphilitic vascular lesions. The cavities were not identical with those seen in the true encephaloclastic porencephaly. Four of his cases, however, showed lesions similar to those described in my group two and it is interesting to notice that in one case some cystic cavities of considerable size were found at such an early age as one month. The child was one of twins and born in breech presentation, similar to one of the cases of my material. Clinically the child showed decerebrate rigidity.

A microcephaly of minor degree is associated with group one in which no patient had a normal circumference of the head. The best developed skulls were found in group three. More than two-thirds of these patients had a circumference above 20 inches and several of them had normal measurements. All of the patients had a circumference above 18 inches.

As far as our material is concerned, the mental deficiency was serious in the majority of cases. Nineteen of the twenty-four were in the idiot group, four

in the imbecile group and only one patient was a moron. Although this observation is of some interest, our material may not be considered as representative for the whole problem. Too few higher grade mentally deficient children were studied to allow conclusions regarding the importance of birth injuries of minor degree or recovery with minor defects.

VI. SUMMARY

1. Although the various mechanisms of birth injuries and their immediate effects are well understood, there is little agreement with regard to the late effects of intracranial hemorrhages upon the development of the infant brain. There seem to be two main reasons for the existing disagreement. The first one is the fact that very few investigators have approached the problem from more than one angle. The material was either clinical or pathological and only in a few instances could the clinical material be supplemented by post-mortem examinations.

The second source of disagreement is the fact that several authors have studied Little's disease with regard to the question whether this condition is mainly due to birth injuries or to antenatal developmental disorders. It is true that if a large group of cases of cerebral spastic infantile paralysis is examined without further differentiation of the various types, a higher percentage of these cases is caused by congenital anomalies than by trauma at birth. There is, however, no justification for neglecting the thirty to forty per cent of post-traumatic cases because of the fact that fifty to fifty-five per cent are congenital malformations.

2. In order to determine accurately the share of congenital malformations and birth injuries in an unselected group of mentally deficient patients, the author has made a study of a hundred autopsies of various types of mental deficiency. After separating the three groups, the idiots, the imbeciles, and the morons, a critical analysis was made of each group separately. The result of this study was, that in the idiot group thirty to thirty-five per cent were due to birth injuries. In the imbecile group only eight per cent were found. It was not possible to determine the importance of birth injuries for the high grade defectives (morons), because this condition is so overwhelmingly familial that only scattered instances of post-traumatic deficiency can be found.

3. The subject of the present study was a determination of the influence of a birth trauma upon the development of the infant's brain. A study of twenty-four cases of traumatic mental deficiency revealed that the pathology can be divided into three main groups: a. Mantle sclerosis or granular atrophy; b. Cystic Degeneration; c. Diffuse Cortical Devastation. These groups overlap each other since small cysts are also found in the first and third groups, while mantle sclerosis can be the end result of cystic degeneration, but as a whole the morbid process represents three separate entities which can be easily recognized.

4. Mantle sclerosis or granular atrophy is the result of subcortical encephalomalacia with reactive brain gliosis and mesenchymal organization. In this condition the cortex itself is mainly destroyed. The leptomeninges are thickened covering the defect of the cortex. The gray matter is gliotic with only

islands of nerve cells left separated by strands of scar tissue. The white matter is spongy-like with formation of cavities which are filled with mesenchymal meshwork and surrounded by gliotic webs. Although the morbid process starts with the traumatic destruction of cortical tissue the condition is progressive due to the fact that scar formation and leptomeningeal fibrosis, including a fibrosis of the arachnoid villi and obstruction of the sagittal sinus lead to interference with the venous drainage and absorption of spinal fluid. There is evidence of edema of the white matter and gradual enlargement of the lateral ventricles with hydrocephalus. According to the age at which the patient dies brain tissue may be destroyed to a large extent with the remaining tissue sclerotic. Mantle sclerosis occurs sometimes in older people after thrombosis or in arteriosclerosis of the brain vessels. In infancy the condition is seen in congenital syphilis, equine encephalitis, other types of encephalitis including toxoplasmosis, but the majority of cases is due to hemorrhagic or anemic necrosis or sinus thrombosis after birth injuries.

5. Cystic degeneration of the brain is a condition which occurs only in infancy. Although single cysts may be found in adults, these cysts are well walled off and the adult brain does not show a tendency to cystic degeneration with complete degeneration of the white matter. The cystic degeneration can be produced by various factors. Trauma, anoxemia, encephalitis and syphilis seem to be the most important etiological factors. Several of the case histories of children who showed cystic degeneration of the brain indicated the existence of long-lasting asphyxiation during birth. It is therefore suggested that asphyxiation with anemic necrosis is the most important factor in the pathogenesis of this condition.

6. The patchy cortical devastation represents a pathological entity which has not yet been thoroughly understood. Examination of sixteen cases of that type showed that the cortical lesions were associated with small areas of hemorrhagic or anemic necrosis in central parts of the brain, thus suggesting that the origin of this condition was due to venous hemorrhages, vasoparetic stasis and anoxia. Patchy devastation of the cortex may be also produced by small infarcts in malignant hypertension, syphilis and tuberculosis in older children, most of them being in the teen-age. In babies and infants, a difficult birth is the main factor in producing the combination of anoxia and trauma which causes this condition.

7. An analysis of the etiological factors shows that practically all modes of birth contribute to birth injuries. It is therefore suggested that it is not the type of birth but several contributory factors which facilitate the occurrence of cerebral hemorrhages. Some of the most important factors are prematurity, breech presentation and long-lasting labor before delivery.

8. A clinical analysis of the cases revealed that epileptic seizures after birth and in early childhood are of foremost diagnostic value for the recognition of cerebral damage. Neurological disorders of a motor and sensory type rank second in significance. Severe mental deficiency is associated with the neurological disorder in the majority of cases.

9. A retrospective study of the cases, which were verified by post-mortem examination, indicated that the diagnosis of cerebral damage at the time of birth can be made in the majority of cases immediately after birth. In the remaining cases the possibility of a cerebral damage was indicated a few weeks after birth and only in a few cases could the diagnosis not be made before the lapse of several months. The material indicates that careful observations on the part of the pediatricians will reveal the seriousness of these cases in the first three months of life. Considering the poor prognosis of the infant with cerebral hemorrhages, it is suggested that close medical attention and neurosurgical intervention should be carried out at the earliest date.

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VII. APPENDIX

SELECTED CASE REPORTS

Group I

Case 1. (37/11). R. G. Both parents were said to be in good health. The father was thirty-three and the mother thirty-four years of age when our patient was born. One older sibling was said to be normal. R. G. was born as the second of dizygotic, dissimilar twins. The twin sister was perfectly normal, and was in high school when the patient died. No peculiarity was observed until he was about five or six months of age, when he did not notice anything going on about him. At the age of eighteen months he had six convulsions in one day.

When admitted to the Wrentham State School in 1926, at the age of three years, R. G. was a poorly nourished and underdeveloped child with a weight of $21\frac{1}{2}$ pounds and a body height of $34\frac{1}{4}$ inches. His hands were thin and claw-like. He rolled his body and head from side to side, sucked his fingers, and made peculiar motions with his hands. He made no effort to sit up. Circumference of head was $47\frac{1}{2}$ cm. ($18\frac{7}{8}$ "), length 16 cm., and width 13 cm. The pupils were round, equal, and reacted to light. Patellar reflexes were not obtained.

The patient lived for twelve years in the institution without mental development as a bedridden, idiotic child, who was noisy and untidy. His physical health was fair.

At the time of his death at the age of fifteen years he was a well-developed but extremely emaciated boy. At autopsy the circumference of the head was 48.8 cm. (19.3"). Testicles were not descended. Pubic hair was not developed. Sex organs were infantile. The head was irregular in shape, with the left side more developed than the right. The dura was not adherent to the skull. The brain appeared soft and did not completely fill the cavity. Its weight was 1150 gm.

Brain after fixation: The leptomeninges were grayish in color and easily stripped off in large pieces without damage. Most striking was the absence of blood within the vessels, which were hardly recognizable. The brain was brownish-yellow in color, and resembled wax. The surface of the convolutions appeared soft, in spite of the fact that the brain had been fixed for more than a year. The fissural patterns of the frontal lobes appeared normal.

The brain was dissected in frontal sections. The lateral and third ventricles were enlarged. At the level of the basal ganglia, the globus pallidus appeared much brighter in color than the putamen, and showed no differentiation. The structures of the internal capsule and the thalamus appeared confused, especially on the right side. The most conspicuous abnormality was found about both occipital lobes, but the right occipital lobe was still smaller than the left one. On the right side the whole occipital lobe, including the medial surface, was microgyric and sclerogyric, showing granular atrophy of the convolutions. On the left side the granular atrophy was not as widespread as on the other side, but was also definite.

Microscopic study: The microscopic study showed a definite lack of myelination of the globus pallidus on both sides and focal demyelination within the white matter. The myelination of the thalamus was also incomplete. There was, however, one myelinated plaque within the thalamus. The convolutions showed atrophy and fibrosis of the leptomeninges. The cortical capillaries were sclerotic, dilated, and congested. There was perivascular demyelination along the pathways of the long veins of the white matter. The terminal vein was much dilated on the right side and filled with blood. Perivascular fibrosis and gliosis were present. Both veins of the fornix were also greatly dilated and fibrotic. The choroid plexuses of the lateral and third ventricles were atrophic. There was widespread capillary fibrosis of the temporal lobes with cellular atrophy within the dentate fascia of the hippocampus. The amygdalar nucleus of the right side showed patchy loss of cells. Both globi pallidi had lost almost their whole myelination.

Subcortical encephalomalacia was present about the occipital lobes. The myelinated core was degenerated and atrophic. The convolutions were shrunken and areas of devastation were marked. In the grey matter a few glia scars were present.

A study of the spinal cord revealed no developmental abnormality. There was marked demyelination, especially in the posterior columns and on the periphery.

Pathological diagnosis: Subcortical encephalomalacia of both occipital lobes with sclerogyrria and microgyria. The morbid process followed the patterns of occlusion of the occipital branches of the posterior cerebral arteries. The abnormality of the basal ganglia was also most striking in the areas of distribution of branches of the posterior cerebral arteries. There was, however, in addition, general cortical atrophy and vasoparetic congestion, perivascular sclerosis, demyelination, and areas of cortical cellular devastation.

Case 2. (41/75). J. B. Both parents were said to be in good health, and were twenty-five years old at the birth of our patient, who was the first of four pregnancies. Two of the younger siblings were normal boys, while one pregnancy terminated in a miscarriage due to albuminuria during pregnancy.

J. B. was born in 1924, at least six weeks premature. According to another source, he was three months premature. Instruments were used. Cerebral hemorrhage was noted three days after birth.

The patient was always backward, and could not walk alone. He was, however, able to stand with help, and at the age of five years he started to talk, although speech was slurred and unintelligible. The legs were underdeveloped and very spastic, drawn up, and could not be straightened. The knee jerks were hyperactive. There was bilateral Babinski. Most of the time the boy sat in a chair and listened intently to everything going on about him. His vision was very poor, but he could recognize everybody by their voices and call people by name. There was alternating internal strabismus, nystagmus, and optic atrophy of both eyes. Both arms showed choreatic athetoid movements. The head was slightly microcephalic, with a circumference of $46\frac{1}{2}$ cm. ($18\frac{1}{4}$ "), length of skull 15 cm., and width of 13 cm.

Patient died at the age of almost eighteen years. At autopsy it was noticed that the left pupil was asymmetrical in shape and the iris broader on the lateral side than on the medial. The pupil had an oval shape with a lengthwise diameter of 6 mm. The other pupil (right) was round, with a diameter of 5 mm. The legs showed paraplegia with atrophy. Circumference of the calves was 12 cm. The elbow joints were flexed. The hands and wrists were bent and the hands were in a claw-like position. There was marked kyphoscoliosis and deformity of the vertebrae. The calvarium appeared asymmetrical. The brain did not entirely fill the brain cavity, and there was a large space between calvarium and dura. The brain weighed 788 gm. The convolutions upon the frontal lobes showed definite granular atrophy with microgyria and sclerogyrria. The microgyria was most marked on the upper part and on the medial surface of both occipital lobes. Both occipital lobes were so atrophic that the cerebellum protruded as a rather huge organ beneath the small cerebral hemispheres. Microscopic examination showed granular atrophy of both occipital lobes with cystic degeneration of the white matter ("Peripheral porencephaly," Schwartz; "encephaloclastic porencephaly," Yakovlev).

The cortex showed general atrophy with fibrosis of the leptomeninges. There was increased myelination of the gray matter (myelinated plaques) and there were areas of cellular devastation. The fascia dentata of the hippocampus showed marked loss of cells and demyelination. There were some gliotic scars spread over the cortex. The putamen showed status marmoratus at the outer border along the external capsule. The vessels of the putamen were enlarged and fibrotic. The lateral ventricles were enlarged.

No developmental abnormality of the spinal cord could be found.

Pathological diagnosis: Granular atrophy and cystic degeneration in the course of both posterior cerebral arteries. Enlargement of the ventricles. Vasoparetic congestion of the cortex with areas of devastation in the gray matter and demyelination of white matter. Status marmoratus of the putamen. Gliotic scars in temporal lobes. Degeneration of the hippocampus.

Case 3. (42/98). E. A. Patient was of Portuguese ancestry. Father was twenty-three years of age at the birth of the patient and was considered fairly intelligent. The mother was married at the age of fourteen and was seventeen at the birth of our patient. Her morality and mentality were somewhat dubious. Our patient was born at home, full term normal labor, the mother being attended by a midwife. Two days after birth, epileptic seizures were observed which lasted for a period of ten days. A doctor who was called in made the diagnosis of cerebral hemorrhage. At the age of six months the child fell from a table on her head and she was said to have been unconscious for some time. After that accident she began to have convulsions again. Her eyesight became progressively poorer. At the age of two years another period of convulsions was observed. She never was able to walk or to stand. She could not talk, but uttered some words.

At the age of three years she was taken to an orthopedic clinic where the diagnosis of spastic paraplegia was made. She showed some athetoid move-

ments of the hands. Patellar reflexes were increased. The left leg was shorter than the right. Her eyes revealed definite trophic changes of the disks, alternating strabismus, peculiar motions of the eyes with the right turning outwards and the left rolling upwards.

The patient lived for eight years in our institution, a large crippled, idiotic girl, who became increasingly helpless because of osteomalacia with deformity of the vertebrae and several spontaneous fractures of her legs.

Autopsy revealed a microcephalic head with a circumference of 45.5 cm. (18"). The dura was adherent to the calvarium. The brain did not entirely fill the cavity. The weight of the whole brain, including the cerebellum, was 498 gm. The cerebellum was of normal size and normally developed. The brain showed almost complete destruction of both occipital lobes. On the left side there was only some sclerotic microgyric bloody tissue left. The border of the destruction was along the parieto-occipital fissure. The right hemisphere was markedly smaller than the left one, and the microgyria and sclerogryria involved parietal and temporal lobes. The occipital lobe was almost completely destroyed.

Microscopic examination of the spinal cord revealed no developmental abnormality.

Pathological diagnosis: Granular atrophy of both occipital lobes and the right parietal and temporal lobes. Lesions were along both posterior cerebral arteries with involvement of some branches of the medial cerebral artery on the right.

Group II

Case 6. Father was a salesman in good health, thirty-eight years of age at the birth of the patient. Mother was thirty-seven years old. She was in good health, a high school graduate, and a former bank clerk. Two siblings were born before our patient. There was no history of stillbirths or miscarriages. Patient was born in 1933, birth weight seven pounds, two ounces, full term. Observations immediately after birth were not recorded. At the age of five months it was noticed that the child had spasms with tremors and trembling. At eight months she had a series of convulsions. At nine months she was admitted to a children's hospital. She was listless and seemed perfectly contented to lie in bed. She did not hold her bottle or play with toys. She could not hold up her head. The convulsions increased in frequency and severity. At first she had from four to five attacks daily, but at the end of the ninth month she had ten attacks daily. They occurred day and night and were generally tonic and clonic. They lasted fifteen to twenty seconds and were not followed by sleep.

On examination the patient appeared a fat baby with a small head and a blank expression. The head circumference was 43 cm. (17"). No pathological reflexes were found. The deep reflexes were hyperactive. Ventriculoencephalogram showed markedly enlarged asymmetrical lateral ventricles, the left being particularly dilated. There was also a considerable amount of air about the periphery. Total protein 23 mg.%.

At the time of admission to the Wrentham State School at the age of eleven months, a peculiarly shaped head with flattened occiput and raised vertex was observed. The vision was impaired. She could not sit up even supported. Hands were held with thumbs turned in on the palms. During her stay in the institution the child was a helpless idiot.

She died at an age of three years, five months. Body length was then 90 cm. Arms and legs were spastic. Right hand was in a grasping position. Legs were abducted in a frog-like position. Head circumference measured 44 cm. ($17\frac{1}{4}$ "), length 15.4 cm., width 11.8 cm. The skull was thin and irregular. In the right temporal region of the brain there were two areas of depression. There was a similar area on the left side. When touched, the dura fluctuated. There was a large space between dura and leptomeninges filled with fluid, and there were smaller pockets filled with fluid beneath the leptomeninges. On a horizontal section at the level of the upper edge of the corpus callosum, a large cystic cavity was discovered in the left hemisphere, filling the whole parietal and occipital lobes. The cavity was divided by fibrous cordst. On the right side of the parietal lobe there was another cavity divided by numerous fibrous cords. The occipital area showed sclerogyrria and microgyria. A horizontal section at the level of the basal ganglia disclosed two large cavities in the left hemisphere, which filled the parietal-occipital and frontal lobes. Although the cavities had destroyed the white matter, a small rim of gray matter remained. Grossly, the basal ganglia appeared intact. Some of the cavities had no connection with the ventricular system. Another small cavity was present in the cerebellum.

The spinal cord showed no developmental abnormality.

Pathological diagnosis: Cystic degeneration of the brain. "Encephaloclastic porencephaly."

Case 7. Father was an intelligent business man thirty years of age when the patient was born. The mother was an intelligent woman twenty-six years of age at the birth of the child. Her condition was good until the seventh month of pregnancy, when she developed a considerable degree of swelling of arms and legs. Our patient was the only child. No stillbirths or miscarriages were recorded. The child was born after prolonged labor which was complicated by a prolapsed cord. As a result the child was asphyxiated before she could be delivered by forceps, and hardly breathed for three hours. During the first week slight spasticity of arms and legs which increased when the baby grew stronger was noticed. She did not cry until after a week, though even then the sounds were abnormal. She took very little food, and only after much patience on the nurse's part. The head circumference was 34 cm. ($13\frac{1}{2}$ ") at birth. Length of body was 50 cm. The child appeared lethargic, listless, pupils contracted, and the extremities showed marked spasticity after a few weeks. She was admitted to a children's hospital less than three weeks after birth because of general spasticity. The baby's condition improved gradually as far as respiration was concerned, but she became increasingly spastic, and acted like a decerebrate animal. Diagnosis: Spastic paraplegia, intracranial injury. The

oculist found the vitreous humor cloudy with intra-ocular hemorrhages in each eye. After three months the vitreous humor became more clear, but no pupillary reaction was noted.

The patient was admitted to the Wrentham State School at the age of six months. It was noted that she tended to lie with feet crossed. There was paraplegia of arms and legs. The head was round, with a circumference of 37 cm. ($14\frac{1}{2}$ "), length 11.7 cm., width 11.3 cm. Bilateral nystagmus. Pupils were small and reacted sluggishly to light. There was no response to objects brought close to the eyeball. The patient had petit mal seizures practically every day and some grand mal. She died at the age of two years, three months.

At autopsy the head appeared markedly microcephalic, because the circumference had not increased since the first measurements at the age of six months were taken. The body was small, with a length of 65.5 cm. The legs were stretched and abducted, and resisted flexion.

The removal of the calvarium was difficult because the dura was adherent. The brain was extremely small, weighing only 250 gm., including the cerebellum which weighed 60 gm. The convolutions were small and irregular. The whole convexity was sheathed in a grayish-white fibrotic arachnoid with much fluid in the sub-arachnoid space. On horizontal section the white matter showed many cavities of varying sizes which were crossed by fibrous cords. The occipital lobes were microgyric and sclerogyric. The basal ganglia showed small holes. The lateral ventricles were greatly enlarged. There was no connection between the ventricular system and the brain cysts.

Microscopic examination: A few of these cavities were real holes, and most of them were filled with a fine fibrous meshwork. The glia cells were regularly distributed in a circle around these holes and formed symmetrical pattern. Where the holes were large, the fibrous meshwork had disappeared and a cavity filled with fluid was present. In myelin-stain preparations, the corpus callosum radiation was well-developed and the optic radiation easily recognizable in its whole length towards the occipital pole. The convolutions contained myelinated cores. The patches of softening with necrosis and cavity formation were most marked in the lateral parts of the white matter. The cortex showed a fairly normal architecture with differentiation of the architectonic layers and normal fissuration. A large number of the nerve cells were, however, found destroyed, and streaks devoid of nerve cells were visible. The surrounding cells were in a stage of disintegration, and all types of ischemic changes, atrophy, swelling and displacement of protoplasm toward the periphery were observed.

Spinal cord showed no developmental abnormality.

Pathological diagnosis: Cystic degeneration of the brain. "Encephaloclastic porencephaly."

Case 8. The father was thirty years of age and the mother nineteen at the birth of our patient. There were two younger children who were said to be normal. Parents were of average intelligence. Our patient was born two weeks prematurely, and weighed $5\frac{1}{2}$ pounds. Birth was instrumental. The grandmother noted some time later that the head of the child was drawn back-

At the time of admission to the Wrentham State School at the age of eleven months, a peculiarly shaped head with flattened occiput and raised vertex was observed. The vision was impaired. She could not sit up even supported. Hands were held with thumbs turned in on the palms. During her stay in the institution the child was a helpless idiot.

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The spinal cord showed no developmental abnormality.

Pathological diagnosis: Cystic degeneration of the brain. "Encephaloclastic porencephaly."

Case 7. Father was an intelligent business man thirty years of age when the patient was born. The mother was an intelligent woman twenty-six years of age at the birth of the child. Her condition was good until the seventh month of pregnancy, when she developed a considerable degree of swelling of arms and legs. Our patient was the only child. No stillbirths or miscarriages were recorded. The child was born after prolonged labor which was complicated by a prolapsed cord. As a result the child was asphyxiated before she could be delivered by forceps, and hardly breathed for three hours. During the first week slight spasticity of arms and legs which increased when the baby grew stronger was noticed. She did not cry until after a week, though even then the sounds were abnormal. She took very little food, and only after much patience on the nurse's part. The head circumference was 34 cm. ($13\frac{1}{2}$ ") at birth. Length of body was 50 cm. The child appeared lethargic, listless, pupils contracted, and the extremities showed marked spasticity after a few weeks. She was admitted to a children's hospital less than three weeks after birth because of general spasticity. The baby's condition improved gradually as far as respiration was concerned, but she became increasingly spastic, and acted like a decerebrate animal. Diagnosis: Spastic paraplegia, intracranial injury. The

oculist found the vitreous humor cloudy with intra-ocular hemorrhages in each eye. After three months the vitreous humor became more clear, but no pupillary reaction was noted.

The patient was admitted to the Wrentham State School at the age of six months. It was noted that she tended to lie with feet crossed. There was paraplegia of arms and legs. The head was round, with a circumference of 37 cm. ($14\frac{1}{2}$ "), length 11.7 cm., width 11.3 cm. Bilateral nystagmus. Pupils were small and reacted sluggishly to light. There was no response to objects brought close to the eyeball. The patient had petit mal seizures practically every day and some grand mal. She died at the age of two years, three months.

At autopsy the head appeared markedly microcephalic, because the circumference had not increased since the first measurements at the age of six months were taken. The body was small, with a length of 65.5 cm. The legs were stretched and abducted, and resisted flexion.

The removal of the calvarium was difficult because the dura was adherent. The brain was extremely small, weighing only 250 gm., including the cerebellum which weighed 60 gm. The convolutions were small and irregular. The whole convexity was sheathed in a grayish-white fibrotic arachnoid with much fluid in the sub-arachnoid space. On horizontal section the white matter showed many cavities of varying sizes which were crossed by fibrous cords. The occipital lobes were microgyric and sclerogyric. The basal ganglia showed small holes. The lateral ventricles were greatly enlarged. There was no connection between the ventricular system and the brain cysts.

Microscopic examination: A few of these cavities were real holes, and most of them were filled with a fine fibrous meshwork. The glia cells were regularly distributed in a circle around these holes and formed symmetrical pattern. Where the holes were large, the fibrous meshwork had disappeared and a cavity filled with fluid was present. In myelin-stain preparations, the corpus callosum radiation was well-developed and the optic radiation easily recognizable in its whole length towards the occipital pole. The convolutions contained myelinated cores. The patches of softening with necrosis and cavity formation were most marked in the lateral parts of the white matter. The cortex showed a fairly normal architecture with differentiation of the architectonic layers and normal fissuration. A large number of the nerve cells were, however, found destroyed, and streaks devoid of nerve cells were visible. The surrounding cells were in a stage of disintegration, and all types of ischemic changes, atrophy, swelling and displacement of protoplasm toward the periphery were observed. Spinal cord showed no developmental abnormality.

Pathological diagnosis: Cystic degeneration of the brain. "Encephalo-elastic porencephaly."

Case 8. The father was thirty years of age and the mother nineteen at the birth of our patient. There were two younger children who were said to be normal. Parents were of average intelligence. Our patient was born two weeks prematurely, and weighed $5\frac{1}{2}$ pounds. Birth was instrumental. The grandmother noted some time later that the head of the child was drawn back-

wards. At one month the child started having convulsions and had frequent seizures for several weeks. It was generally expected that he would die. There was difficulty in breathing, with spells of cyanosis of the face. Complete paralysis of the arms and legs and head developed, so that the child could not eat and had to be fed with a tube for three months. At a hospital the child's condition was attributed to a cerebral thrombosis at birth.

At the age of two and one-half years the child was admitted to the Wrentham State School. He was a small, helpless boy with bilateral nystagmus. Pupils did not react to light. The lips were cold and cyanotic. The child ground his teeth. There were hyperactive reflexes and spasmodic spasticity of extremities and body. At that time the child weighed only thirteen pounds. The face was like a mask. The body was as stiff as a piece of board, and remained that way even when supported only by one hand beneath the back. The picture was that of decerebrate rigidity with all muscles in a condition of contraction. Through the thin skin, the contracted muscles were easily recognizable, and the child's body resembled an illustration of human musculature. He lived for two more years in this helpless condition, and then died at the age of four years. At that time the body length was 75 cm., circumference of head was 42.2 cm. ($16\frac{1}{2}$ "). The pupils were enlarged and measured 9 mm. in diameter. The musculature appeared hypertrophic, like that of an athlete. The body was completely stiff. The calvarium appeared asymmetrical. When the dura was opened more than 1000 cc. of spinal fluid escaped from the opening. The whole brain cavity was found almost empty; only on the base of the skull, the basal ganglia were found and some tissue remnants of the temporal lobes. The cerebellum appeared huge in contrast to the shrunken brain hemispheres. The whole central nervous system weighed 132 gm. The spinal cord revealed no developmental pathology.

Pathological diagnosis: Cystic degeneration of brain with a few sclerogyrlic remnants about the temporal and occipital lobes.

Group III

Case 10. Family history was negative. The boy was the only child, born in June, 1934. Birth was full term, but prolonged, instrumental, hard labor. Peculiarity was noticed immediately after birth when the muscles stiffened and the child bled from nose and mouth. He never learned to walk or talk. The child's legs were limp and gave way when he was put on his feet.

At the age of two years, eleven months, he was admitted to the Wrentham State School. It was noticed at that time that he cried in a shrill tone. He was unable even to hold up his head unsupported. He had odd, stertorous breathing spells. The breathing was suggestive of that which occurs under deep anesthesia. Two days after admission the child died, after having had very definite convulsive seizures and sinking rapidly into coma. The lumbar puncture made a few hours before his death revealed a negative Wassermann, total protein of 15 mg.%, total chloride 850 mg.%. No cell increase.

The body of the child measured 96 cm. Head circumference was 49 cm.

(1914"). The calvarium adhered tightly to the skull. In the region of the vertex an old, organized hemorrhage was found with resulting depression of brain tissue. Another old organized hemorrhage was found about the right hemisphere near the calcarine fissure and the occipito-parietal fissure. At both of these places the underlying brain tissue was depressed. The dura was like rough sandpaper to the touch. Weight of the brain was 1000 gm. The cerebellum appeared well-developed, but was somewhat adherent to the tentorium, which presented an area of bluish discoloration measuring more than one-half inch in diameter.

Microscopic examination revealed sinus thrombosis of the sagittal sinus with many small thrombi in the tributary vessels. There were many minute hemorrhages into the cortex. Both lateral ventricles were enlarged. Scattered over the whole cut surface of the frontal sections were small, dark colored spots which represented blood vessels with fibrotic enlarged walls, enlarged perivascular spaces, and exudation into the surrounding tissue. The blood vessels were tightly filled and greatly enlarged. The thalamus was degenerated on both sides and the nerve tissue replaced by gliosis. The choroid plexuses were found thrombosed and markedly degenerated. The putamen showed status marmoratus. The cortex revealed many small areas of devastation. The cortical capillaries were enlarged and fibrotic. The central white matter showed patchy demyelination along the course of the veins. Degeneration of the hippocampus was conspicuous.

The spinal cord showed no developmental abnormality, but the vessels were in a state of paretic dilation with ensuing congestion.

Pathological diagnosis: Residues of subdural and intraleptomeningeal hemorrhages. Sinus thrombosis of sagittal sinus. Vasoparetic stasis. Congestion of the tributaries of the vena magna. Enlargement of the vena terminalis with perivascular necrosis. Degeneration of the choroid plexus. Necrosis of the putamen with reactive status marmoratus at some levels. Patchy cortical devastation. General vascular sclerosis.

Case 11. Family history was negative. There were seven siblings older than the patient who were said to be normal. During the second month of pregnancy with S. C. the mother was in an automobile accident. One report indicated that she had worn a brace for a spinal injury, but it is not known whether or not this followed the accident mentioned above. The patient was a full term normal delivery, but was a "blue baby." She had never been well since birth, and had a long history of indefinite vomiting with much difficulty in keeping food down. Along with the vomiting attacks, the child would cry and become cyanotic, with ensuing rigidity of the whole body. These attacks were numerous on some days, and bore no relationship to meals. The patient was admitted to the Wrentham State School at the age of seven years. She was extremely untidy, uncooperative, and difficult to care for. She did not react to any questions or comments and showed very little interest in things going on about her. She made purposeless movements with her arms and was able to walk around with a clumsy gait. The reflexes were hyperactive. Cir-

cumference of head was $46\frac{1}{2}$ cm. ($18\frac{1}{4}$ "). She died at the age of seven years, six months.

At time of autopsy she was a well-nourished but small, under-developed child with a body weight of 38 pounds and a length of 110 cm. The hands were small, the fingers small and thin. The legs were outstretched and the feet in an equinovarus position. There was much spasticity of knee and ankle joints. The dura adhered to the skull. It appeared thickened, showed many spots of bluish discoloration. The leptomeninges were found highly congested. The brain weighed 870 gm. The veins of the Sylvian fissure were much congested and the whole region appeared dark bluish in color.

Microscopic examination revealed extreme cortical congestion with all capillaries tightly filled with blood and enlarged. The perivascular tissue was sclerotic and the brain tissue necrotic. The cortex showed many areas of devastation. The leptomeninges were fibrotic and congested. All the ventricles were enlarged. The surroundings of the third and fourth ventricles showed gliosis and congested vessels with many smaller recent hemorrhages. In the dentate nucleus of the cerebellum there was an area of softening.

The spinal cord was negative.

Pathological diagnosis: Diffuse brain atrophy with dilation of the ventricular system. Diffuse cortical devastation. Vasoparetic congestion. Capillary fibrosis. Perivascular necrosis and demyelination.

Case 12. Family history was negative. Our patient was born in 1932. The child was delivered by an elective Caesarian and there was considerable difficulty in resuscitation. Birth weight was 5 pounds, 6 ounces. Although the child cried very little during the first three months the parents were not concerned until the child failed to sit up. At the age of two years the child could not sit up, nor had she made any attempt to talk. At that time she was admitted to a children's hospital. She was a well-developed, idiotic child. Her eyes followed light only occasionally. There was marked hypermobility of all joints. Fingers were long and tapering. X-ray showed pronounced enlargement of lateral and third ventricles and a marked excess of air over the periphery.

The patient was admitted to the Wrentham State School at the age of two years, four months. Her height was 35 inches, weight $21\frac{1}{2}$ pounds. Circumference of the head was 47 cm. ($18\frac{1}{2}$ "). Her behavior was restless and resistive. She cried during the entire examination and showed general tremors of the head and peculiar movements of the arms. The head appeared flattened at the crown, especially on the right side and in back. Frontal bosses were prominent. Pupils were unequal, the right being slightly larger than the left one. She did not stand or walk. The reflexes were only slightly increased. She died at the age of five years, nine months.

The autopsy showed a nice-looking, well-developed child of about six years with a body length of 103 cm., and a head circumference of 48 cm. The arms were bent and slightly spastic. The legs were flabby, and the thighs abducted. The feet were stretched out and slightly spastic. The brain did not completely fill the brain cavity. There was a rather large space between brain and cal-

varium, and much spinal fluid came out when the dura was opened. Brain weight was 1220 gm. It appeared asymmetrical. The right occiput was more depressed than the left. The brain was extremely congested. All the veins of the periphery were filled with dark blue blood. The leptomeninges were thickened. There was some fluid in the sub-arachnoid space. There were many small hemorrhages on the surface of the brain.

Spinal cord was negative.

Pathological diagnosis: General atrophy of the brain with enlargement of the ventricles. Areas of devastation were found all over the cortex. Leptomeningeal fibrosis. Extreme vasoparetic stasis with perivascular fibrosis and necrosis. Multiple small hemorrhages, old and recent.

Case 13. History of father indicated instability and occasional alcoholism. Mother was of average intelligence. She was at a lying-in hospital six times for delivery by Caesarian section, because of a contracted pelvis through which it would have been impossible to deliver a living child. Her first child was normal. The second died ten hours after birth because of prematurity. The third child was stillborn, anencephalic. The fourth and fifth children were normal. The sixth child, our patient, was also delivered by Caesarian section, after her birth the mother was sterilized. Our patient was at first considered normal, but at the end of the first year it was noticed that she could not lift her head.

At the age of two years she was seen at the Wrentham State School Out-Patient Department, where internal strabismus was noted. The child was cheerful and playful, but made purposeless motions with arms and legs and was unable to walk. At the age of three years she learned to walk. She vomited very frequently.

A. R. was admitted to the Wrentham State School at four years of age. She walked about in an aimless manner, sucking her thumb continuously. She showed no interest in her surroundings, and did not talk. Her body length was 3 feet, weight $21\frac{1}{2}$ pounds. Circumference of head was 47 cm. ($18\frac{1}{2}$ "). Epileptic seizures were observed at the age of eight years. At that time she did not seem to walk quite as well as she had before, and was not interested in anything. She had epileptic seizures frequently after that time. At thirteen years of age seven to fifteen seizures were recorded monthly. These increased up to thirty-two during some months. The patient died at the age of fifteen years, eight months.

At autopsy the body measured 132 cm. Circumference of the head was 48.1 cm. The body was normally developed for its age. Removal of the calvarium was extremely difficult because of the tight adhesions between dura and calvarium. The brain appeared greatly congested, small, and did not fill the brain cavity. It weighed 955 gm.

Spinal cord was negative from a developmental point of view, but showed degeneration of the pyramidal tracts.

The pathological diagnosis was almost identical with that of Case 12, (38/16). The cortex showed vasoparetic congestion and stasis with vascular fibrosis and

perivascular necrosis, patchy devastation and demyelination in the course of the vessels, general atrophy of the brain, the left hemisphere smaller than the right. There was leptomeningeal fibrosis. The basal ganglia showed asymmetry between right and left. The putamen showed slight status marmoratus. A few myelinated plaques were found in the thalamus.

Case 14. (38/21). D. E. Both parents were young, normal, well-to-do people. Our patient was the third child, delivered by high forceps, with a birth weight of 6 pounds, 2 ounces. Child had a prominent caput succedaneum, and was resuscitated with difficulty. Development was slow. He was a feeding problem, and at six months developed spells featured by refusal of food and difficulty in swallowing. He cried frequently in a high-pitched voice, ate poorly with frequent regurgitations and drooling.

X-rays of the skull at the age of two years showed considerable symmetrical dilation of the ventricles with evidence of cortical atrophy. Physical examination showed a rather enlarged head with prominent frontal bosses, active reflexes, and positive Babinski.

Neurological examination at the age of three years revealed a head circumference of 50.5 cm. (19.1"). Shape of head was slightly indicative of hydrocephalus. The arms and hands were hypotonic, but the arm reflexes active. When the child became more excited, purposeless motions with tremor and athetosis were observed. The legs were bent at the hip and knee joints. Musculature was flabby. Knee and ankle jerks were increased. Babinski was present on both sides. The child did not sit up. The legs were completely paralyzed. Spastic paraplegia. The mental attitude was listless. No reaction to light or sound.

The patient died at the age of three years, four months. At autopsy the brain appeared large, with dilated ventricles, and weighed 1300 gm. The results of the microscopic examination were identical with those of the two cases previously described. The outstanding features were the extreme cortical vasoparetic congestion and diffuse cortical atrophy with widespread areas of devastation and perivascular demyelination. The mesenchymal tissue showed extreme fibrosis.

Spinal cord was negative, from a developmental point of view.

Case 15. (38/30). M. C. Family history was non-contributory. There were three normal living siblings, two older and one younger than our patient. Another child died of meningitis. M. C. was born in 1915. There was little information about the birth, which was said to have been normal, or about her behavior during the first few weeks of life. It is, however, definitely known that she had convulsions when about five weeks old. Peculiarity was first noticed when she failed to sit up or to attempt to walk. The head was flattened in the back and the patient rolled from one side to the other. Convulsions were again observed at the age of two years. Patient was examined in our school at the age of four years. She had internal strabismus and inequality of the pupils. The head appeared broad. At the age of six or seven years she learned to walk alone, and after that time she was able to wander about. She fed herself, but was never able to talk. Her general development was much

retarded, and at the age of nine she did not appear much more than four years of age. Her gait was always a little unsteady and hesitant. After the age of thirteen, she had epileptic seizures and periods of crying which were considered epileptic equivalents. The seizures became increasingly frequent, and many attacks were observed monthly. At twenty-three and one-half years she died in an epileptic status which lasted four days, and which was interrupted only for short periods.

At autopsy the calvarium was extremely heavy. The frontal bone measured 1.5 cm. in thickness. The brain did not entirely fill the brain cavity, and a space of about one-half inch was found between brain and dura. The leptomeninges were of grayish-white color. There was an increase of fluid in the sub-arachnoid space. The brain weighed 1040 gm. There were many small hemorrhages upon the convexity, some recent, but some well-organized. The lateral ventricles were enlarged.

Microscopic examination: The brain was dissected in frontal sections. A hemispheric section at the level of the optic chiasm revealed a striking difference between the right and left sides. The left caudate nucleus was well-developed, but the capillaries were congested and there was one large myelinated plaque in the rostral lateral part of the caudate nucleus. The larger vessels were tightly filled and enlarged. There was some perivascular necrosis and some sub-ependymal gliosis along the lateral wall of the lateral ventricle. The internal capsule and the putamen were fairly normal. Both veins of the septum pellucidum were greatly enlarged and bulged into the ventricles. On the right side the caudate nucleus was reduced to less than half of its normal size and the lateral ventricle was enlarged according to the reduction of the caudate nucleus. Beneath the ependymal wall there was a large area of softening and necrosis which was partly organized through some mesenchymal septa. The internal capsule was interrupted, partly demyelinated, and contained a cystic cavity. At the foot of the internal capsule, its structure was confused with that of the globus pallidus, which was reduced to a mass of myelinated fibers. The putamen showed an increase in myelination. Its vessels were greatly enlarged and filled with blood. The vessels at the base of the brain, between the temporal lobe and the basal ganglia, were also enlarged and congested. The cortex of the frontal and temporal lobes showed striking capillary fibrosis. The convolutions were atrophic and covered with fibrotic leptomeninges in which large and tightly filled vessels were suspended. Some vessels were thrombosed. The gray matter showed areas of devastation and confusion of the architecture, and the white matter showed perivascular demyelination.

On the next hemispheric section at the level of the anterior commissure, the left side showed about the same structure as described before. The globus pallidus was larger at this level, but the division in two parts was confused. The vena terminalis was enlarged, and perivascular necrosis and gliosis conspicuous. The veins of the septum pellucidum were partly thrombosed. The anterior commissure showed areas of necrosis and demyelination. On the right side, the reduction of the caudate nucleus was conspicuous, and the sub-ependymal necrosis more extended. Some thrombotic vessels were found.

The globus pallidus was larger, but definitely disorganized. The putamen showed one area of necrosis and some increase in myelination in the lateral portion. The vessels were enlarged, and perivascular necrosis was conspicuous. The cortex showed the same congestion all around. Especially striking was the leptofibrosis about the gyrus cinguli on the right side, where the atrophic cortex showed some scar formation around the hyperemic thrombosed vessels. A similar picture was noticeable around the temporal lobes. Here the areas of devastation and necrosis were marked.

On the next frontal section, about 5 mm. behind the last, the sub-ependymal necrosis on the right side and its relationship to the vena terminalis was evident. The necrosis involved the globus pallidus. The internal capsule was interrupted and partly demyelinated. At this level, subependymal necrosis was also recognizable on the left side in relation to the vena terminalis. The globus pallidus was disorganized. The picture of the cortex was the same as described before.

On the next level, through the columns of the fornix, the abnormality of the basal ganglia was less marked, but dilation of the venae terminales and their tributaries, and perivascular necrosis were conspicuous. The cortex was atrophic and large thrombosed vessels covered the convolutions.

At the level of the beginning of the optic tracts the structure of the basal ganglia was almost normal, but the interruption of the internal capsule on the right side and lesions in the anterior and lateral nuclei of the thalamus were conspicuous. The choroid plexuses were partly atrophic, and the vessels greatly enlarged.

At the level of the mammillary bodies a large area of degeneration with mesenchymal organization was found in the medial nucleus of the thalamus, and in the massae intermediae. The surroundings of the third ventricle were gliotic. The vena terminalis on the right side was thrombosed and showed perivascular fibrosis. The cortex showed the same picture all around as described above.

Spinal cord showed no developmental abnormality.

Pathological diagnosis: Cortical atrophy. Vasoparetic congestion and capillary fibrosis. Leptomeningeal fibrosis. Enlargement of lateral ventricles. Extensive sub-ependymal necrosis along the vena terminalis on the right side. Necrosis in the thalamus of the left side.

Case 16. (40/52). M. W. Parents were normal and in good health, with the exception of high blood pressure which the mother developed during pregnancy with the patient. M. W. was the older one of two children, the sister being normal. The birth was premature, induced by bagging on account of the mother's high blood pressure. No information about the early history was available. Patient was born in 1928. Backwardness was noticed when the child made no effort to walk or talk. At the age of six years convulsions were observed. At that time she had a peculiar and awkward gait, walking on her toes. She also had the habit of shaking her hands from the wrists.

M. W. was admitted to the Wrentham State School at the age of six years, at which time she appeared to be a well-developed, well-nourished, restless,

clumsy, and awkward child. Her posture was remarkably poor. She had an asymmetrical face. Reflexes were hyperactive. Circumference of head was 49.5 cm. (19 $\frac{3}{4}$ "). She had apparently no epileptic seizures between 1934 and 1939, when seizures again occurred, and these continued at irregular intervals until the time of her death in 1940, at the age of twelve years, four months.

At autopsy M. W. was a well-developed girl with a body length of 140 cm. and a head circumference of 50 cm. (20"). The brain weighed 1124 gm. The sub-arachnoid space about the convexity was cloudy. There was atrophy of the brain with deepening of the sulci. The brain showed patchy thickening of the leptomeninges, with increase of the vessels, which were enlarged and partly thrombosed. The underlying convolutions were depressed and submerged. The cortex was atrophic. In the region of the right vena terminalis the ependymal wall was lifted and there was some sub-ependymal necrosis. All the tributaries were enlarged and tightly filled with blood. The lateral ventricles were enlarged ex vacuo. There was another hemorrhagic region in the thalamus.

Spinal cord showed no developmental abnormality.

Pathological diagnosis: Brain atrophy with leptomeningeal fibrosis. Vaso-paretic congestion of cortex. Devastation and perivascular demyelination. Sub-ependymal softening and enlargement of right vena terminalis. Hemorrhagic necrosis in thalamus.

Case 17. (42/78). S. M. Both parents were above average, both in intelligence and social standing. One older child was normal. The birth of our patient in 1939 was said to have been a full term normal delivery, with a birth weight of 6 $\frac{1}{2}$ pounds. The private obstetrician who delivered the child considered the birth uneventful. The child's retardation was not recognized until several months after birth, when she failed to show any interest in her surroundings, and did not sit up. She was seen in a children's hospital at the age of two years, when she had a convergent strabismus. Head circumference was 46 cm. (18 $\frac{1}{4}$ "). Spinal fluid was normal. Encephalogram showed blunting and enlargement of the lateral and third ventricles, most marked in the posterior horn of the left lateral ventricle. There was excessive subarachnoid and a small amount of subdural air.

The child was admitted to the Wrentham State School in 1941, at the age of two years and seven months. She was a helpless and fussy child, who played a little with toys but soon lost interest and dropped them easily. Her height was 30 inches and her weight 23 pounds. She was an attractive child, although her facies was slightly asymmetrical. She had alternating internal strabismus. The right pupil was slightly larger than the left, and both reacted sluggishly to light. The skull was very asymmetrical, and laterally posteriorly flattened. There was slight cyanosis of the nail beds. The knee jerks were hyperactive. Epileptic seizures were not reported, but the child died suddenly five months later at the age of two years, ten months. She became suddenly cyanotic and gasped for breath.

At autopsy the calvarium appeared extremely thin. The brain was large and was found pressing against the calvarium. It weighed 950 gm.

Micro-copic examination: The cortex showed an extreme degree of vaso-

The globus pallidus was larger, but definitely disorganized. The putamen showed one area of necrosis and some increase in myelination in the lateral portion. The vessels were enlarged, and perivascular necrosis was conspicuous. The cortex showed the same congestion all around. Especially striking was the leptofibrosis about the gyrus cinguli on the right side, where the atrophic cortex showed some scar formation around the hyperemic thrombosed vessels. A similar picture was noticeable around the temporal lobes. Here the areas of devastation and necrosis were marked.

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Spinal cord showed no developmental abnormality.

Pathological diagnosis: Brain atrophy with leptomeningeal fibrosis. Vaso-parietal congestion of cortex. Devastation and perivascular demyelination. Sub-ependymal softening and enlargement of right vena terminalis. Hemorrhagic necrosis in thalamus.

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At autopsy the calvarium appeared extremely thin. The brain was large and was found pressing against the calvarium. It weighed 950 gm.

Microscopic examination: The cortex showed an extreme degree of vaso-

The globus pallidus was larger, but definitely disorganized. The putamen showed one area of necrosis and some increase in myelination in the lateral portion. The vessels were enlarged, and perivascular necrosis was conspicuous. The cortex showed the same congestion all around. Especially striking was the leptofibrosis about the gyrus cinguli on the right side, where the atrophic cortex showed some scar formation around the hyperemic thrombosed vessels. A similar picture was noticeable around the temporal lobes. Here the areas of devastation and necrosis were marked.

On the next frontal section, about 5 mm. behind the last, the sub-ependymal necrosis on the right side and its relationship to the vena terminalis was evident. The necrosis involved the globus pallidus. The internal capsule was interrupted and partly demyelinated. At this level, subependymal necrosis was also recognizable on the left side in relation to the vena terminalis. The globus pallidus was disorganized. The picture of the cortex was the same as described before.

On the next level, through the columns of the fornix, the abnormality of the basal ganglia was less marked, but dilation of the venae terminales and their tributaries, and perivascular necrosis were conspicuous. The cortex was atrophic and large thrombosed vessels covered the convolutions.

At the level of the beginning of the optic tracts the structure of the basal ganglia was almost normal, but the interruption of the internal capsule on the right side and lesions in the anterior and lateral nuclei of the thalamus were conspicuous. The choroid plexuses were partly atrophic, and the vessels greatly enlarged.

At the level of the mammillary bodies a large area of degeneration with mesenchymal organization was found in the medial nucleus of the thalamus, and in the massae intermediae. The surroundings of the third ventricle were gliotic. The vena terminalis on the right side was thrombosed and showed perivascular fibrosis. The cortex showed the same picture all around as described above.

Spinal cord showed no developmental abnormality.

Pathological diagnosis: Cortical atrophy. Vasoparetic congestion and capillary fibrosis. Leptomeningeal fibrosis. Enlargement of lateral ventricles. Extensive sub-ependymal necrosis along the vena terminalis on the right side. Necrosis in the thalamus of the left side.

Case 16. (40/52). M. W. Parents were normal and in good health, with the exception of high blood pressure which the mother developed during pregnancy with the patient. M. W. was the older one of two children, the sister being normal. The birth was premature, induced by bagging on account of the mother's high blood pressure. No information about the early history was available. Patient was born in 1928. Backwardness was noticed when the child made no effort to walk or talk. At the age of six years convulsions were observed. At that time she had a peculiar and awkward gait, walking on her toes. She also had the habit of shaking her hands from the wrists.

M. W. was admitted to the Wrentham State School at the age of six years, at which time she appeared to be a well-developed, well-nourished, restless,

clumsy, and awkward child. Her posture was remarkably poor. She had an asymmetrical face. Reflexes were hyperactive. Circumference of head was 49.5 cm (19½"). She had apparently no epileptic seizures between 1934 and 1939, when seizures again occurred, and these continued at irregular intervals until the time of her death in 1940, at the age of twelve years, four months.

At autopsy M. W. was a well-developed girl with a body length of 140 cm and a head circumference of 50 cm (20"). The brain weighed 1124 gm. The subarachnoid space about the convexity was cloudy. There was atrophy of the brain with deepening of the sulci. The brain showed patchy thickening of the leptomeninges, with increase of the vessels, which were enlarged and partly thrombosed. The underlying convolutions were depressed and submerged. The cortex was atrophic. In the region of the right vena terminalis the ependymal wall was lifted and there was some sub-ependymal necrosis. All the tributaries were enlarged and tightly filled with blood. The lateral ventricles were enlarged ex vacuo. There was another hemorrhagic region in the thalamus.

Spinal cord showed no developmental abnormality.

Pathological diagnosis: Brain atrophy with leptomeningeal fibrosis. Vaso-paetic congestion of cortex. Devastation and perivascular demyelination. Sub-ependymal softening and enlargement of right vena terminalis. Hemorrhagic necrosis in thalamus.

Case 17 (42/78) S. M. Both parents were above average, both in intelligence and social standing. One older child was normal. The birth of our patient in 1939 was said to have been a full term normal delivery, with a birth weight of 6½ pounds. The private obstetrician who delivered the child considered the birth uneventful. The child's retardation was not recognized until several months after birth, when she failed to show any interest in her surroundings, and did not sit up. She was seen in a children's hospital at the age of two years, when she had a convergent strabismus. Head circumference was 46 cm (18¼"). Spinal fluid was normal. Encephalogram showed blunting and enlargement of the lateral and third ventricles, most marked in the posterior horn of the left lateral ventricle. There was excessive subarachnoid and a small amount of subdural air.

The child was admitted to the Wrentham State School in 1941, at the age of two years and seven months. She was a helpless and fussy child, who played a little with toys but soon lost interest and dropped them easily. Her height was 30 inches and her weight 23 pounds. She was an attractive child, although her facies was slightly asymmetrical. She had alternating internal strabismus. The right pupil was slightly larger than the left, and both reacted sluggishly to light. The skull was very asymmetrical, and laterally posteriorly flattened. There was slight cyanosis of the nail beds. The knee jerks were hyperactive. Epileptic seizures were not reported, but the child died suddenly five months later at the age of two years, ten months. She became suddenly cyanotic and gasped for breath.

At autopsy the calvarium appeared extremely thin. The brain was large and was found pressing against the calvarium. It weighed 950 gm.

Microscopic examination. The cortex showed an extreme degree of vaso-

paretic congestion with capillary and leptomeningeal fibrosis. The cortical layers showed devastation and the white matter demyelination along the course of the straight veins. The lateral ventricles were enlarged and the corpus callosum very thin. The venae terminales were tightly filled with blood, enlarged, and there was an area of sub-ependymal necrosis upon the anterior nucleus of the thalamus on the left side. The posterior horn of the left lateral ventricle was greatly enlarged and showed slight ependymal proliferation.

The spinal cord showed no developmental abnormality.

Pathological diagnosis: Cortical atrophy with vasoparetic congestion. Capillary and leptomeningeal fibrosis. Patchy devastation and demyelination along the course of the straight veins. Enlargement of the lateral ventricles. Reduction of corpus callosum. Dilation and perivascular necrosis in the region of the venae terminales. Marked degeneration of the dentate fascia of the hippocampus. Areas of softening and degeneration in the cerebellum.

Case 19. The family history was non-contributory. There were four children older than our patient, all considered normal. Our patient, Margaret, was a high forceps delivery, labor lasted eighteen hours, and the patient received lacerations about the face and forehead with moulding of the head. Development was slow and retardation became conspicuous when child failed to sit up or to take notice of her surroundings. She did not learn to walk or talk. She wet and soiled her bed and clothing. When she was admitted to the Wrentham State School at an age of three years and seven months, she was a pale and rather good looking youngster who could not sit up. She had marked frontal bosses and a depressed lower forehead. She clapped her hands and uttered peculiar noises like a six months old baby. She died at an age of twelve years of intestinal trouble.

The brain was small weighing 980 gms. Along the sagittal sinus there were many residues of epiduras hemorrhages, especially about the precentral region. The leptomeninges were partly fibrotic. Microscopic examination revealed patchy areas of devastation spread all over the cortex. Leptomeningeal fibrosis. The lesions were identical with those described in detail in previous case records.

Case 21. The father was a clergyman and both parents were considered of high intelligence. There were four brothers and two sisters, all of them normal. Patient was a full term baby and there is no report available about birth and early infancy. He had several convulsions in early life. The peculiarity was noticed when he failed to develop like other children, and it became more and more conspicuous when the boy did not talk. He learned, however, to walk. He remained a low grade boy with a mental age of only 1 year and six months. When he died at an age of twenty-nine, the brain was unusually heavy, weighing 1650 gms. This was due to some increase in fluid. The brain was dissected in frontal sections and stained by numerous standard methods. Microscopic examination revealed cortical atrophy with focal devastation, focal leptomeningeal fibrosis, enlargement of the lateral ventricle and atrophy of the caudate nucleus. The central white matter showed marked demyelination.

PLATE I

FIG. 1 (Upper left). Case 3, a female child who died at an age of thirteen years. Superior view of both hemispheres. The left occipital lobe shows granular atrophy with sclerosis of the convolutions and shrinkage. The convolutions in front of the lesion are of normal size and show normal vascular patterns. The lesion corresponds to the distribution of the posterior cerebral artery. The right hemisphere shows destruction to a greater extent. The occipital pole is destroyed in the same way as on the left side but the lower parts of the parietal and central convolutions are also destroyed. The whole hemisphere is smaller than the left side but the intact convolutions are of normal structure. The lesions on the right side correspond to the distribution of the posterior and medial cerebral arteries.

FIG. 2 (Upper right). The same case, view from behind. Note the sclerogyrus convolutions at the edge of the lesion. These small "microgyric" convolutions are the product of atrophy and are not to be confused with true microgyria, as a result of antenatal developmental pathology.

FIG. 3 (Bottom). At the left, Case 5, a female child who died at an age of 7 years, 11 months. The right hemisphere is atrophic and sclerotic with enlargement of the lateral ventricle. The left hemisphere appears better developed but is covered with thickened leptomeninges and is of soft consistency. Clinically, the child showed quadriplegia. Microscopic examination revealed in addition to the lesion of the right hemisphere, cystic lesions in the left hemisphere. The morbid process was caused by complete obstruction of the sagittal sinus, and not by arterial occlusion.

The brain at the right is from Case 4, a male who died at an age of twenty-two years. The lesion is restricted to the left hemisphere which showed complete mantle sclerosis. The right hemisphere was fairly well developed. Clinically, the patient had a right hemiplegia but developed remarkable skill with his left hand and foot, and was able to talk.

PLATE II

FIG. 4 (Upper left). Brain of Case 7, a female child who died at the age of two years. Note the hemorrhagic, fibrotic organized leptomeninges about the superior frontal lobes and both central convolutions.

FIG. 5 (Upper right). Myelin stain of thalamus, insula and Sylvian fissure. Note the smaller and larger cysts in the subcortical layers of the insula. The cortex is still well preserved except immediately above one larger cyst. Myelination is incomplete.

FIG. 6 (Center left). Section through another level of basal ganglia. The internal capsule is partly destroyed. The lateral ventricle is enlarged. Some of the subcortical cysts are filled with a fine fibrotic meshwork.

FIG. 7 (Center right). Myelin stain demonstrating the cysts in the white matter. The small cysts are filled with meshwork but in the larger cysts the fibre strands are ruptured or displaced to the edge and the cysts are filled with fluid. There is no connection with the lateral ventricle.

FIG. 8 (Lower left). Horizontal section through brain of the same case. Note the many cysts of different sizes in the right hemisphere but also in the left hemisphere. Both lateral ventricles are greatly enlarged.

FIG. 9 (Lower right). Horizontal section through brain of Case 6, a female infant who died at an age of three years. At this level two large cysts are recognizable, one filling the whole temporal lobe and one in the right frontal lobe. The cysts show some fibrotic meshwork. The cortex about the cysts is degenerated but small remnants are still recognizable. The leptomeninges are greatly thickened about the cystic wall and there is no communication with the subdural space.

PLATE III

FIG. 10 (Top). Sagittal section through the brain of Case 12, a female infant who died at the age of six years. Note the normal leptomeninges (on the left side) about the occipital region. On the right side, the central and frontal convolutions are covered with greatly thickened leptomeninges in which large blood vessels are suspended. The subarachnoid spaces are filled with hemorrhagic organized tissue. The convolutions are partly suppressed especially the post central convolution "epileptogenic" lesion—Penfield. The frontal convolutions are tilted and flattened.

FIG. 11 (Center). Case 16. Sagittal section through one hemisphere. Note the same situation as in Figure 10. The occipital lobe is free of lesions but the leptomeninges about the pre-central and frontal convolutions are greatly thickened. There are many suppressed convolutions and the subarachnoid spaces are filled with organized hemorrhagic tissue. The suspended vessels are enlarged and congested. There are also hemorrhages in the thalamus and in the subependymal tissue on the floor of the lateral ventricle. The vessels of the lateral ventricle are enlarged and congested. In the fresh specimen, residues of subependymal hemorrhages were recognizable.

FIG. 12. (Bottom). Part of frontal cortex of Case 15. Myelin stain. Note the central demyelination in the white matter and the bulb-like enlargement of the myelinated cores in two convolutions. The gray matter shows areas of atrophy recognizable by the grayish white color. There are many patchy areas of devastation.

PLATE IV

THREE FRONTAL SECTIONS THROUGH BRAIN OF CASE 15. MYELIN STAIN

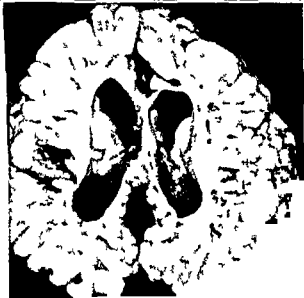
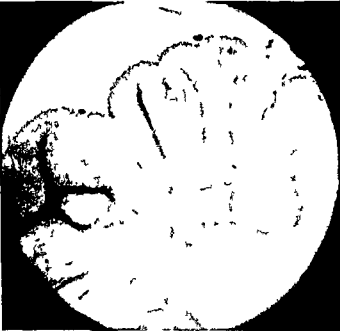
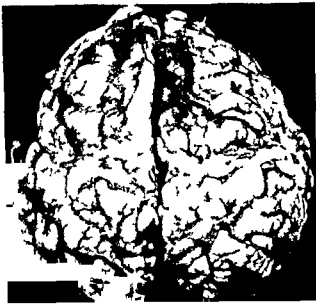
FIG. 13 (Top). Shows a section at the level of the anterior commissure. The right lateral ventricle is enlarged due to depression of the caudate nucleus. There is a subependymal necrosis all along the ventricle wall. The tissue shows some fibre meshwork in which the enlarged terminal vein and its branches are suspended. The internal capsule is interrupted and blotted out. There is one cyst within the internal capsule.

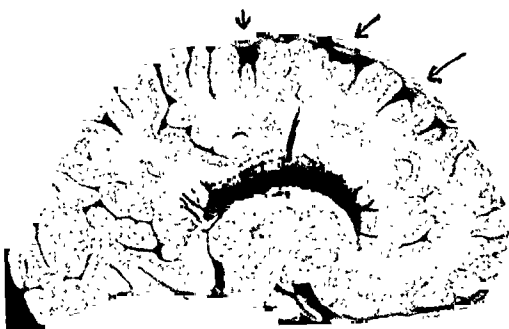
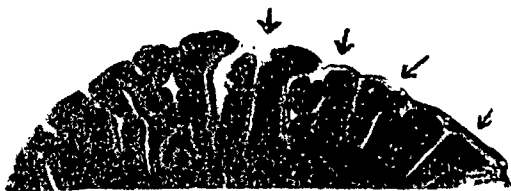
The surroundings of the left terminal vein show some necrosis. Note also the fibrotic leptomeninges on the right gyrus cinguli above the corpus callosum.

FIG. 14 (Center). Frontal section more caudal to Figure 13. The subependymal necrosis on the right side is marked. The internal capsule is partly blotted out and shows smaller necrotic areas which are also seen in the globus pallidus. At this level there is also subependymal necrosis on the left side and the terminal vein appears thrombosized. Both lateral ventricles are enlarged and are asymmetrical.

FIG. 15 (Bottom). Frontal section at the level of the mammillary bodies. There is a large cyst filled with meshwork in the left thalamus and a smaller one above the third ventricle. The frontopontine tracks on the left side are demyelinated. The pallido-subthalamic fibres are also degenerated on that side.









DIABETIC NEUROPATHY

GENERAL REVIEW WITH REPORT OF 125 CASES*

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CONTENTS

	PAGE
Introduction.....	111
Selected case records.....	113
General clinical data.....	121
Neurologic symptoms.....	124
Neurologic signs.....	125
Spinal fluid.....	127
✓Gastro-intestinal disfunction.....	127
Genito-urinary and sphincter disturbances.....	130
Peripheral autonomic nerve disease.....	132
Orthostatic hypotension and orthostatic tachycardia.....	133
Association of diabetic neuropathy and retinopathy.....	136
Peripheral vascular disease.....	139
Vitamin B deficiency and diabetic neuropathy.....	143
Diagnosis.....	148
Etiology.....	150
Treatment.....	151
General considerations.....	152

The occurrence of a characteristic type of peripheral nerve disorder in patients with diabetes mellitus has long been recognized. The earliest description has been credited to Marchal de Calvi who in 1864 (1) observed pains of sciatic distribution and peripheral areas of anesthesia in diabetic patients and introduced the idea that neurologic lesions were the result of diabetes mellitus rather than the cause of this disorder. In 1881, Boucard (2) called attention to the frequent absence of tendon reflexes in diabetics. In closely succeeding years there were many case reports published particularly in the French literature. In 1885 Althaus (3) described in detail the clinical symptoms of diabetic neuropathy noting in some cases the close similarity to those of tabes dorsalis. In the same year Leval-Picquechef (10) introduced the term pseudotabes and Pavy (4) in his description of the neuritic symptoms of diabetics noted lightning pains, exquisite cutaneous hyperesthesia, and the nocturnal intensification of the neuritic symptoms. Pryce (5, 6) and Leyden (7) both in 1887 reported cases with necropsy findings and associated the neurologic abnormalities with disease of the peripheral nerves. Pryce's patient had perforating ulcers, ataxic symp-

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toms and the "glossy skin" described by Sir James Paget (5) as occurring in patients with peripheral nerve disorders. Leyden (7) proposed a clinical classification for peripheral nerve disease in diabetics as follows: 1) hyperesthetic or neuralgic form, 2) motor or paralytic form, and 3) ataxic or pseudotabetic form with peripheral sensory deficiencies, absent tendon reflexes, and absent pupillary reflexes. He reported 2 cases which although running a chronic course improved with dietary management. Auché in 1890 (8) gave an extensive review of previous work, added new cases to the literature, and attempted to reproduce experimentally the nerve lesions by injecting into them concentrated sugar solutions. Buzzard (9) compared the neuropathy of alcoholism with that of diabetes, noted evidence of degeneration of peripheral autonomic nerves, and found therapeutically that modification of the diet to achieve a reduction in the glycosuria was of definite benefit. Charcot (10) compared the neuritic manifestations of alcoholism, diabetes, and beri-beri, noted the complicating vascular lesions in diabetes, and described the steppage gait associated with foot drop. Other references to the early literature as well as to publications appearing as late as 1935 are given by Jordan (11).

The neurologic complications of diabetes mellitus were thus clearly recognized more than 50 years ago. A perennial interest has since been manifested but, as noted by the late Kinnier Wilson (12), little has been added to the observations of the early writers. In spite of the advancing knowledge in recent years regarding the nature and treatment of diabetes, including its complications, the subject of diabetic neuropathy has become more confused. There has been little agreement as to the etiologic factors, even a definite relationship to the natural history of diabetes has never been proved. The clinical characteristics are not well known, the diagnosis often being prefixed by "so-called" or "questionable," and many have agreed with Jolliffe (13) who designates "diabetic" neuropathy a misnomer. Clinicians have recognized of course that other types of peripheral nerve disease such as those due to metallic poisoning, acute infection, trauma, etc., might occur fortuitously in patients with diabetes and that these should not be designated as diabetic in etiology. As to neuritic disease of less specific origin, several factors peculiar to the diabetic have complicated the problem of diagnosis and clinical investigation. Diabetes occurs in all degrees of severity, at different ages, and the clinical course is of many years duration. Diseases more or less intrinsically associated with diabetes may supervene. Peripheral vascular disease for example which is common in diabetics past middle age may be associated with neuritic symptoms. Some clinicians for this reason have considered diabetic neuropathy a "senile" degenerative change resulting from the sclerosis of peripheral arteries. Again, since the treatment of diabetes nearly always entails dietary modification there have been attempts, especially during the present era of expanding knowledge regarding the rôle of vitamins in nutrition, to demonstrate nutritional deficiencies in such diabetics as develop evidence of peripheral nerve disease. Apart from these factors, however, many have suspected that a specific neuropathy more intimately associated with the disordered metabolism of diabetes mellitus exists.

A recent influx of patients with diabetes and associated neuropathy on the Medical Wards of the University Hospital has provided first-hand clinical experience with the condition and has led me to review the accumulated information dealing with the subject. In addition to the cases currently available for study the hospital records of all patients having this diagnosis registered in the 7 year period following July 1, 1936, were analyzed. The cases reported here have thus all been seen during a period subsequent to the major advances in diabetic management and in diagnostic methods, as well as the availability of such therapeutic agents as protamine zinc insulin, purified vitamins, etc. In all there were 125 among the somewhat more than 3000 new diabetic patients seen during the 7 year period in whom the diagnosis of diabetic neuropathy appeared to be based on adequate study and examination. Thirty-five of these, including all of the cases reported in detail, have been studied personally. Patients in whom the diagnosis was questionable or who had other extensive disease such as massive gangrene, metastatic neoplasm, cerebral arteriosclerosis, etc. were not included. There were no patients with pernicious anemia or chronic alcoholism in the group.

It will be apparent from the discussion to follow that most diabetics who develop organic disease of the peripheral nerves have had antecedent periods usually of months or years duration of grossly neglected or poorly managed treatment. There is strong evidence that the disordered metabolism of diabetes mellitus itself is the etiologic factor in this as well as other accompanying diabetic complications. Severe polyneuropathy may be precipitated, sometimes acutely, after periods of diabetic neglect by common infections, surgical procedures, or other events notorious for aggravating the severity of diabetes. Not only may the peripheral motor and sensory neurons be involved but spinal nerve roots, autonomic pathways concerned with temperature regulation, postural blood pressure adjustment, vasomotor control, intestinal and bladder function as well. Difficulties in diagnosis and problems in treatment will be discussed. Five cases of special interest will first be presented in detail.

CASE REPORTS

The first case is presented as a typical instance of mild to moderately severe peripheral neuropathy appearing after a few months' neglected treatment of a comparatively mild diabetes.

M. G., #521512. This 49 year old, married saleswoman was first admitted to the hospital on March 8, 1943, complaining of diabetes and infected toes. Her general health had been excellent until June, 1942, at which time undue fatigue, increased thirst, and polyphagia led to medical consultation and her first urinalysis which revealed a heavy glycosuria. In retrospect a slow loss of weight from 196 to 156 pounds had been noted during the preceding 3-4 years. Her physician diagnosed diabetes, outlined a diet, and advised the use of insulin. The latter, however, was refused and she obtained elsewhere a preparation to take orally as a substitute for insulin. Subsequent urine examinations continued to show heavy glycosuria. In July, 1943, her weight decreased another 20 pounds. Her weakness compelled her to resign her position. Her legs began to ache and cramp, the calf muscles became sore, and sweating over the feet

and legs became less. There were occasional sharp, shooting pains in the lower legs. Chronic constipation developed for the first time and "double strength" laxatives were needed constantly.

She developed a severe upper respiratory infection 3 months before admission which persisted 2-3 weeks. At this time her feet began to feel cold and numb, especially at night and after exposure to low temperatures. Her fingers became numb, tingled, and clumsy to the extent that sewing was difficult. Six weeks before admission she began to use a hot pad nightly to keep her feet warm and alleviate a dull, aching pain that kept her from sleeping. Her gait became unsteady, it seemed as if she "walked on pegs," and her ankles swelled. Five days before admission her right great toe became discolored and the lower leg blistered, which the patient attributed to a burn from the electric pad. When the toe became a dark purple in color and pus exuded from under the toenail, hospitalization was sought.

Physical examination showed a well developed woman with evidence of recent weight loss. The pupils were small, round, equal in size, and reacted better to light than accommodation. The optic fundi were free of hemorrhages and exudates. Her skin was clear, the tongue pink and without papillary atrophy. The biceps, triceps, and left patellar reflexes were weakly obtained, the right patellar and achilles reflexes were absent. The vibratory sense was slightly impaired over the lower extremities. Superficial pain and tactile sensibilities were diminished over the great toe and deep peroneal distribution on the left, with almost complete anesthesia in the comparable area on the right. There was increased muscle tenderness. Pus exuded from under the right great toenail and the skin over the tips of the first two toes was gangrenous. The feet were warm, normal in color, and the dorsalis pedis and posterior tibial arterial pulses were strong.

Urinalysis showed a "4 plus" glycosuria without ketonuria. The fasting blood sugar on admission was 226 mg. per hundred cc. Blood counts and films were normal. Gastric analysis showed abundant free hydrochloric acid. A starch-iodine sweating test showed striking diminution in sweating over the lateral aspects of the lower legs and absent sweating over the dorsal parts of the feet. Skin temperature studies given in detail below were interpreted as showing no impairment of arterial blood flow in the legs, but partial vasomotor paralysis greater on the right side.

Satisfactory diabetic regulation was obtained on an 1800 calorie diet with 150 gm. carbohydrate and 80 gm. protein, using 10 units of regular insulin, t.i.d. After 4 weeks hospitalization the infected toes had healed and she was symptomatically improved, although there was no definite alteration in the neurologic status.

The second case was chosen as an instance of a severe type of peripheral nerve disease in a young diabetic. The diabetes appeared mild for years but was severely neglected and finally required large amounts of insulin daily for control. An atonic bladder paralysis was present and an extensive, hemorrhagic and proliferating retinopathy developed while he was under observation. An unusually good therapeutic result was eventually obtained.

D.S., #391721. The patient was first admitted to the University Hospital on October 26, 1936 when 14 years old. He had been in good health until 1-2 months before admission when he became unduly fatigued and lost weight. Increased thirst, polyphagia, and polyuria followed. Two days before admission the family physician found glycosuria and advised hospitalization.

Physical examination showed a tall, well developed, school boy, 5 ft. 5 in. tall weighing 94 pounds. There were no significant physical abnormalities. Urinalysis showed a 4 plus glycosuria but no diacetic acid. A glucose tolerance test showed a fasting blood sugar of 148 mg. per hundred cc., and hourly values of 340, 418, and 482 mg. respectively. He was soon eating a 3000 calorie diabetic diet with 155 gm. available glucose. With small doses of

regular insulin t.i.d. the glycosuria cleared. A few days after admission, however, malaise, anorexia, a low-grade fever and jaundice developed and the liver and spleen became palpable. There was complete recovery in 3-4 weeks and it was concluded that he had had entarrhal jaundice. The insulin was gradually withdrawn while he remained aglycosuric. He was discharged 7 weeks after admission on the low carbohydrate diet without insulin and weighing 101 pounds.

Two months later it was found that he could tolerate 170 gm. available glucose in his diet but the urine contained sugar when it was raised to 185 gm. Accordingly the lower carbohydrate value was retained.

He was again admitted to the hospital on July 9, 1937 for tonsillectomy. His height was 5 ft. 6½ in. and his weight 107 pounds. Following the diet with restricted carbohydrate his urine had remained sugar free. A glucose tolerance test after a 5 day preparatory high carbohydrate diet showed a fasting blood sugar of 87 mg. per hundred cc. and hourly values of 204, 296, 250, and 182 mg. respectively. It was considered safe for him to return to a general diet and return for periodic check-ups.

He was not seen again, however, until November 4, 1942. Although his general health had been considered satisfactory until 1 year before, his weight had never exceeded 112 pounds and there had been no weight gain in 2 years. His diet was an unrestricted farm diet including generous amounts of milk, fresh meat, eggs, fruits, and vegetables. The urine had not been examined for over 4 years. About 1 year before admission he had become chronically fatigued and unable to do more than light farm work. Frequent upper respiratory infections, sore, aching muscles, numbness and tingling about the lower legs and feet, and severe "shooting pains" in the lower extremities had appeared and gradually became worse. Three months before admission his ankles began to swell during the day to the extent that wearing shoes was difficult. Low back and flank pain followed the development of a severe upper respiratory infection 5 weeks before admission and shortly afterward polyuria and polydipsia reappeared. Three weeks before admission, micturition became difficult and required straining. He became severely constipated and had no bowel movement for 6-7 days at a time. One week before admission there was a low abdominal bulge. He was catheterized and nearly a quart of residual urine obtained.

Physical examination on admission to the hospital showed a thin, under-nourished, chronically ill boy appearing less than his 20 years of age. His skin was loose and dry. The left pupil was larger than the right but both reacted normally. The optic fundi were normal. The oral hygiene was poor, the tongue red but without papillary atrophy. The liver edge was palpable well below the costal margin. A flaccid bladder was felt rising 4 cm. about the pubis. On catheterization 1100 cc. of residual urine was obtained. The muscles of the extremities were thin, atrophic, and very tender to pressure. There was pitting edema to the knees bilaterally. The biceps, triceps, patellar, and achilles reflexes were absent. There was no Hoffman or Babinski sign. Cutaneous, vibratory, and position senses were not definitely impaired. There was no evidence of impaired peripheral circulation.

Urinalysis on admission showed a 4 plus glycosuria and small amounts of diacetic acid and acetone. The blood cell counts, hemoglobin concentration, and films were normal. The Kahn test was negative. The blood sugar on admission was 416 mg. per hundred cc., the plasma CO₂ combining power 64 volumes per hundred cc. The plasma ascorbic acid was 0.70 mg. and the total serum proteins 7.6 gm. per hundred cc. with 2.6 gm. albumin. The spinal fluid was under normal pressure, clear, and contained no cells. The Pandy reaction was faintly positive, the total protein 69 mg. per hundred cc., the colloidal gold curve 4333210000 and the globulin 4 plus. Cystometric examination showed an atonic bladder paralysis with sense of filling absent, warm and cold sensibility impaired, and a large amount of residual urine.

The patient remained in the hospital 5 months. Diabetic regulation was difficult and very poor for three to four months, partly due to a large residual urine and a severe urinary tract infection that developed. There was no improvement in bladder function in spite

of decompression, tidal drainage and so forth, and before discharge suprapubic cystotomy was required.

Soon after admission punctate retinal hemorrhages and exudates appeared. Six weeks after admission his vision became cloudy and an ophthalmology consultant, finding macular edema, punctate and flame shaped hemorrhages, and extensive areas of exudate, diagnosed severe diabetic retinopathy, O.U. Six weeks later there had developed an extensive proliferating retinopathy with both fundi filled with new-formed, dilated and tortuous veins and capillaries with even more extensive deep and superficial hemorrhages but no further visual impairment.

With diabetic control the liver receded until it was no longer palpable. His diet was supplemented with brewer's yeast, thiamin, niacin and fish liver oil throughout a period of four months. He was discharged little improved and without objective change in the neurologic status. His insulin requirement on a 3000 calorie diet with 200 gm. carbohydrate and 90 gm. protein was 65 units of protamine zinc and 35 units of regular insulin daily.

The patient was seen at intervals for another eighteen months. The diabetes remained well controlled: there was minimal glycosuria, the fasting blood sugar averaged about 100 mg. per hundred cc., and there were no significant insulin reactions. He gradually gained in weight and in strength, and became able to tolerate light activity about the home. In June, 1943, the retinal hemorrhages became less extensive and the pattern of the retinal veins more normal.

Examination on November 17, 1943 showed a gain in weight to 131 pounds. The biceps, triceps, and ankle reflexes were absent, the patellar reflexes weakly present with reinforcement. There was no definite sensory impairment. A cystometric examination showed a sense of filling at 50 cc., a bladder capacity of 425 cc., and no residual urine. Hot and cold sensibilities were intact. An ophthalmology consultant found the retinopathy much improved, reporting only minimal pigmentary disturbance in the regions of former hemorrhage, slight wrinkling and fibrotic scarring in different areas, a few new-formed blood vessels and a rare rosette shaped hemorrhage, "without a doubt the most astounding recovery of a diabetic retinitis of this type and severity I have ever seen or heard of."

After a period of intermittent clamping the cystotomy tube was removed and normal urinary function reestablished. His further clinical course was uneventful.

The third case is that of another young male with moderately severe diabetes, poorly treated for four years, with neuritic symptoms beginning shortly after dietary restrictions were abandoned. Grossly disturbed gastro-intestinal function, an atonic bladder paralysis, and localized neuritic symptoms were present.

H. C., #524359. This 14 year old schoolboy was first admitted to the University Hospital on April 21, 1943 complaining of pain about the scrotum and unregulated diabetes. His general health had been excellent until July 1938, when in a week's time an insatiable thirst, polyuria, and leg cramps appeared. His weight rapidly dropped from 112 to 88 pounds. The family physician found a heavy glycosuria and admitted him to a local hospital for treatment. While there he became aglycosuric, the symptoms abated, and he gained weight. On discharge a measured diet was prescribed and 10 units of regular insulin twice daily.

Three months later he fell from a swing and injured his back. A heavy glycosuria was again found and his family submitted him to chiropractic treatment for both the back injury and the diabetes. During the next four years the urine continued to show 3 and 4 plus reactions for sugar, and polydipsia, polyuria and polyphagia were present most of the time. There was no coma and no known acidosis. The insulin dosage was not increased until 2 years after the onset when 20 units twice daily was given. His weight slowly increased to a maximum of 120 pounds and his height increased 2 inches to 5 feet 7 inches.

In June 1942, during the summer vacation he began doing heavy farm labor. The diabetic diet prescribed 4 years earlier did not satisfy his appetite and he began to eat unrestricted quantities of food. The insulin dosage was not altered. A few weeks later his legs became weak, his feet ached, and he noted that his underwear was frequently wet from urinary dribbling. A month later straining was necessary for urination and his scrotum began to burn painfully. Extremes of temperature produced unusual discomfort. He had frequent night sweats. His bowel movements became loose. Two to five watery, yellow stools containing mucous began to follow every meal, each passage accompanied by cramps and borborygmi. Occasionally sleep would be disturbed by his having to pass eight to ten stools during the night.

The symptoms persisted with variable intensity until late in December 1942, when following a severe upper respiratory infection he became much worse having extreme fatigue, aching, tender muscles, and numbness, prickling and recurrent waves of heat and perspiration in the medial gluteal and perineal regions. Burning pain in the scrotum prevented sleep at night and led to his withdrawing from school. Constipation often with no bowel movement for five to six days at a time began to alternate with the diarrhea. Constant early morning nausea developed and he vomited about one out of three meals.

Physical examination on admission showed the patient to be a thin, undernourished boy in distress due to pain in the scrotal region. The skin was clear, the tongue pink, coated and without papillary atrophy. The pupillary reactions were normal, the fundi free of hemorrhages and exudates. The blood pressure, heart and lungs were not unusual. The liver was not palpable. There was tenderness in the suprapubic region but the bladder was not definitely outlined. Neurologic examination showed generalized muscular weakness and under-development. The triceps and right patellar reflexes were diminished, the left patellar and ankle reflexes absent. There was increased muscle tenderness in the legs and pain on squeezing the achilles tendon. Cutaneous, vibratory, and position senses were well preserved. There was exquisite cutaneous hyperesthesia and tenderness about the perineum and scrotum. The color of the feet was normal, the pedal arteries bounding. Skin temperature studies showed no evidence of occlusive peripheral vascular disease.

Urinalysis on admission showed a heavy glycosuria and a moderate amount of acetone. The blood sugar was 300 mg. per hundred cc. and the CO_2 combining power of the blood 49 vols. per hundred. Blood counts, serology, stool examination, and gastric analysis were all normal. Cystometric examination showed the sense of filling to begin at 450 cc., bladder capacity well over 750 cc. with low expulsive pressure, and sensation to heat present but not to cold. There was no urinary residual. Panendoscopic examination revealed no bladder neck obstruction. The spinal fluid was clear, under normal pressure and showed normal dynamics. There were no cells present, the Pandy reaction was positive, the total protein 80 mg. per hundred cc., the globulin 2 plus positive, the spinal fluid serology and colloidal gold curve both negative. Roentgen examination of the gastrointestinal tract showed free passage of barium into the intestinal loops, 50 per cent gastric retention at 3 hours, 25-30 per cent at 5 hours, with wide scattering of barium throughout the small bowel, "A definite delay both in gastric emptying and in small intestine motility" (F. J. Hodges).

Satisfactory diabetic regulation was attained using a 2200 calorie diabetic diet containing 150 gm. carbohydrate and 80 gm. protein with 60 units of protamine zinc and 20 units of regular insulin daily before breakfast. Shortly before discharge it was demonstrated that procaine injection of the right pudendal nerve temporarily relieved the scrotal pain on one side. This nerve was then surgically divided. He remained, however, uncomfortable throughout his stay of six weeks. Codeine was required daily for the relief of pain. He was discharged unimproved. Three months later he reported by letter that he had had some benefit from the nerve section but that his general condition was unchanged.

The fourth case illustrates again the neglect of diabetic treatment as a factor productive of diabetic neuropathy. Disturbed gastro-intestinal motility and severe orthostatic hypotension were present, in addition to other manifestations of peripheral nerve disease.

W. G., #492561. A 43 year old bread salesman was first admitted to the University Hospital on November 1, 1941, complaining of diabetes, diarrhea, and dizzy spells.

He had "never had a sick day" until six years before admission when lethargy, thirst, polyuria, polyphagia, and loss of weight occurred. He entered a Detroit hospital where a diagnosis of diabetes mellitus was made and a diet and insulin regimen prescribed. Under treatment his symptoms abated. Six to eight months later he began to disregard the diabetes and soon abandoned the diet and the use of insulin. His average weight of 180-190 pounds declined to 155-160 pounds and neither the blood sugar nor urine was analyzed for a period of three to four years. There was no known acidosis.

About two years before admission, some four years after the appearance of diabetes, he became impotent. Several months later weak legs, numbness, tingling, and shooting pains in the extremities, and painful, sensitive skin over the trunk gradually developed. Diarrhea began to alternate with constipation and urination became urgent and frequently uncontrolled. Dizzy spells appeared, occurring especially when assuming an upright position, being worse during the early morning and when fatigued. A few months before admission his diabetic symptoms returned as at the outset and his weight fell to 140 pounds. A diet with insulin was again prescribed but he became more incapacitated and had to stop work. His muscles became tender and sore. His ankles began to swell during the daytime. A low blood pressure was discovered by his physician who, suspecting Addison's disease, referred him to the hospital for diagnosis and treatment.

Physical examination showed a poorly nourished, lethargic, uncomfortable white male. The skin was clear and free of pigmentation. The pupils were small, less than 2 mm. in diameter, equal in size, round and regular. The right one did not react to light, the left one very little, both reacting definitely on accommodation. The tongue was pink and coated. The blood pressure was 100/60 mm. of mercury when recumbent, 80/40 when sitting, 50/? when upright, gradually falling when standing quietly to imperceptible levels and accompanied by faintness or syncope. The skin over the trunk and extremities was painfully sensitive to light touch and pressure. All tendon reflexes were absent. The thigh and calf muscles were exquisitely tender. The plantar responses were flexor although there was pronounced plantar hyperesthesia. The vibratory sense was greatly diminished at the ankles and there was slight blunting of the superficial sensibilities peripherally. The feet were normal in color with easily palpable pulses in the pedal arteries.

Laboratory examination of the blood, stool and urine showed no abnormality except glycosuria. A glucose tolerance curve was typically diabetic. The Kahn test was negative and the spinal fluid was normal except for a total protein of 83 mg. per hundred cc. and a 3 plus globulin. A barium enema showed nothing abnormal. A starch-iodine sweating test showed diminished sweating over the abdomen and thighs and absent sweating below the knees. The Flack test (81), blowing against a column of mercury with the glottis open, caused prompt syncope. The "water test" for Addison's disease (14) did not confirm the suspected adrenal insufficiency.

Diabetic regulation was easily obtained on a 2400 caloric diet containing 200 gm. carbohydrate and 90 gm. protein using 35 units of protamine zinc and 10 units of regular insulin daily before breakfast. The diet was supplemented with brewer's yeast and for a time parenteral thiamin chloride with no definite benefit. The postural hypotension was treated with fair success by elevating the head of the bed at night, added salt to the diet, and with ephedrine and amphetamine. He was discharged little improved after seven weeks hospitalization.

The patient was followed for 16 months, it being necessary for him to spend 19 weeks as an in-patient. The neuritic symptoms, aching and shooting pains, hyperesthesia, muscle tenderness, and so forth, increased considerably in severity for 3-4 months then slowly began to improve. He was unable to work for 7 months. Periods of anorexia and vomiting lasting 2-3 days recurred several times and once persisting for a week necessitated hospital admission and administration of intravenous fluids. The diarrhea became exceedingly troublesome with 8-10 bowel movements daily. Each meal was followed by ab-

dominal distension, painful borborygmi, and the urgent passage of 1-3 loose, yellow stools. He frequently awoke at night with a stool in his pajamas. When last seen his major complaint was diarrhea. Examination showed weight gain and less severe but demonstrable postural hypotension. Tendon reflexes in the upper extremities and at the patellae were obtained with reinforcement but the achilles jerks were absent. Vibratory sense was diminished at the wrists and knees, absent at the ankles. Plantar hyperesthesia, slight muscle tenderness, and peripheral blunting of the cutaneous sensibilities remained.

The fifth case illustrates the diagnostic difficulty present when diabetic neuropathy occurs in a patient with a positive luetic history. Argyll Robertson pupils, abnormal salt metabolism, abnormal postural regulation of blood pressure, and an atonic bladder paralysis were present. The failure of vitamin therapy with relapses in symptoms following loss of diabetic regulation is shown.

T. F., #519430. A 44 year old poultry farmer was first admitted to the University Hospital on January 29, 1943 complaining of diabetes and weak, numb legs. During the first World War while serving with the Polish Foreign Legion he developed a chancre and a positive Wassermann. He was given 20 intravenous and 20 intramuscular injections during 6-8 months. The serology became negative early in treatment and remained so at the time of demobilization over a year later. He enjoyed excellent health then until the spring of 1940 when excessive thirst appeared. A few days later his physician found glycosuria and a fasting blood sugar of "over 300." He was given a "diet card" and instructed to take insulin. Because the first injection produced what was thought to be an insulin reaction an adequate amount of insulin was never taken thereafter. The urine continued to give orange and red reactions with Benedict's reagent and months later a fasting blood sugar of "296" was obtained. His weight dropped from his average 185 pounds to 145 pounds, then gradually rose to hover between 150-160 pounds.

About 1½ years before admission, more than a year after the onset of the diabetes, he began to note cold feet, weak legs with flabby muscles, and shortness of breath on exertion. He was compelled to seek easier work. Loss of libido and later impotence, with neither erections nor ejaculations, developed. He began to crave heavily salted food.

One year before admission his feet and lower legs became dry with absent sweating and his ankles swelled in the daytime. Chronic constipation developed. Severe upper respiratory one of these his calf muscles became very tender and enough to make one scream" radiated into both legs, gradually subsiding in a few weeks time. His family commented on a peculiar look about his eyes—the pupils becoming very small.

Two months before admission a severe sore throat with cough and hoarseness developed following which his weight dropped from 160 to 140 pounds and he became entirely unable to work. His cold feet became numb and felt like "clubs." Continuous tingling "pins and needles" in his lower legs and fingers, and painful, sensitive skin over the trunk appeared. He began to have dizzy spells when standing. The chronic constipation was intensified until no bowel movements occurred without enemas. At the suggestion of his physician he took vitamin capsules daily for 5 weeks but without benefit.

Physical examination on admission showed an undernourished white male. The tongue was coated, reddened at the edges, without papillary atrophy. The nails were brittle.

Examination of the fundi showed atrophy of the optic fundi. The liver edge was palpable 4-6 cm. below the costal margin. The muscles of the extremities were weak, atrophic, and very tender. The gait was unsteady, and there was ataxia on the heel to knee test and tandem walking. The triceps and patellar reflexes were diminished, the biceps and Achilles reflexes were absent. The plantar responses were normal. There was peripheral

blunting of pain and tactile sensibilities and nearly absent vibratory sense at the ankles. The skin over the trunk and soles of the feet was hypersensitive. The feet were normal in color and the arterial pulses bounding.

Laboratory examination of the blood and stools was normal. Urinalysis showed a 4 plus glycosuria and a trace of acetone. The fasting blood sugar was 236 mg. per hundred cc. and the plasma CO₂ combining power 50 vols. per hundred cc. The Kahn test was negative, the spinal fluid normal, and there was no free HCl in the gastric contents after histamine. Total serum proteins were 7.7 gm. with 4.1 gm. albumin per hundred cc. The plasma ascorbic acid was 0.32 mg. per hundred cc. A starch-iodine sweating test showed diminished sweating over the feet and the entire right leg. An electrocardiogram was normal. Cystometric examination showed an atonic bladder paralysis, the capacity well over 800 cc., without sensation to filling, with absent cold and equivocal warm sensibility, and a residual of 50 cc. About two-thirds of the daily urinary output occurred at night, the patient often voiding 1200-2000 cc. at one time on arising in the morning. Skin temperature studies showed no evidence of circulatory inadequacy in the legs, but at low environmental temperatures the skin temperature did not fall as it does when normal vasoconstriction is present.

For a trial period the patient was given just enough insulin to clear the urine of ketones. He became symptomatically improved especially in reference to the muscle tenderness after 2-3 days bed rest. He was then given 1000 mg. thiamin chloride intramuscularly in two weeks time without further subjective or objective improvement. Muscle tenderness remained. He was then regulated on protamine zinc and regular insulin. The blood pressure on different occasions was 106/68 mm. of mercury in the supine position with no change except for a few mm. rise in the diastolic pressure on standing. At a time when glycosuria was minimal added salt was withdrawn from his diet. After two days his weight fell 4 pounds. The blood pressure when supine was 104/60 (pulse 80) with a fall to 80/50 (pulse 120) after standing erect. Salt being resumed ad lib he gained 10 pounds in weight in 24 hours and became obviously edematous. The postural fall in blood pressure and tachycardia disappeared.

With control of the diabetes he slowly improved and after 1 month in the hospital was able to return home. Gain in weight and strength continued. After a short time, however, sugar began to reappear in the urine and small increases in the insulin dosage were inadequate for regulation. Following a week of heavy glycosuria his skin began to feel "raw and burned." Shooting and tingling pains, sore muscles, and extreme weakness reappeared. His weight began to fall rapidly.

On May 5, 1943 he was again admitted to the hospital to stay 7 weeks. His insulin requirement was found to have increased. With proper regulation slow improvement began. 45 gm. of brewer's yeast and 60 mg. of nicotinic acid were added to his daily diet for 6 weeks without observable benefit. During this time a readjustment of his diabetic regimen was inadvisedly attempted, heavy glycosuria and hyperglycemia reappeared. An acute exacerbation of the neuritic symptoms followed. Thiamin pyrophosphate 0.010 gm. daily was given intramuscularly for ten days without observable benefit. Later 70 cc. of crude liver extract was given intravenously over a 4 day period without definite effect immediately or subsequently.

He returned home and during a month's time improved until he could tolerate some light work and of his former symptoms only moderate weakness and tingling in the extremities remained. Then severe constipation appeared acutely. In spite of multiple laxatives there were no bowel movements for three days. With the administration of an enema severe upper abdominal pain began. For five days, during which time all food and even water was vomited, a continuous "sickening" epigastric pain persisted, "like having one's testicles squeezed in a vise." Hypodermics were needed for relief of the pain. He was admitted to the hospital for the third time and shortly afterward the pain abruptly subsided. Roentgen examination of the gastrointestinal tract, blood serology, and the spinal fluid were again all normal. The neurologic condition was unchanged.

One year after his first admission, he reported that nausea and vomiting had not re-

curred and that the shooting pains and hyperesthesia had disappeared although some paresthesias remained. His legs were weak, his muscles ached and became tender with more than a few minutes of exercise, and he could climb steps only with the greatest difficulty.

Passing from individual case histories to the more general consideration of our 125 patients with diabetic neuropathy, the sex incidence was males 69 (55 per cent) and females 56 (45 per cent). On admission to this hospital patients are divided into three economic groups: public welfare, average, and superior. Slightly over half of the group (64, or 51.2 per cent) were welfare patients, 43 (34.3 per cent) were of average means, and 18 (14.5 per cent) were of superior means which is about the average distribution of our patients with diabetes and other diseases. The age incidence and the duration of the diabetes before the onset of the neuropathy is shown in Table I. It is significant that more than

TABLE I

Age of Patients Developing Diabetic Neuropathy and Duration of Preceding Diabetes

YEARS OF AGE	NUMBER OF CASES	INTERVAL BETWEEN ONSET OF DIABETES AND APPEARANCE OF NEUROPATHY	
		Range	Average
17 to 20	8	3 mo. to 6 yrs.	2.9
21 to 25	5	1½ to 7 yrs.	4.0
26 to 30	6	1 to 7 yrs.	5.3
31 to 35	5	1 to 14 yrs.	6.8
36 to 40	9	6 mo. to 9 yrs.	4.9
41 to 45	11	1½ to 9½ yrs.	7.2
46 to 50	15	0 to 24 yrs.	6.2
51 to 55	25	0 to 30 yrs.	7.0
56 to 60	19	2 mo. to 13 yrs.	4.7
61 to 65	11	0 to 7 yrs.	2.7
66 to 70	8	0 to 12 yrs.	2.6
70 or over	3	5½ to 35 yrs.	15.0

a quarter of the patients were less than 40 years of age and 8 were 20 or less. In the average patient diabetes had existed slightly over 5 years before the onset of neuropathy. Under the same conditions of lax diabetic care, to be referred to in detail below, the young do not appear to have greater immunity from developing neuropathy than those of older age groups, and the previous duration of the diabetes is not greatly different for any age period. In some cases, however, neuritic symptoms and evidence of organic disease of the peripheral nerves occurred early in the disease. In nine of our cases neuritic symptoms rather than the classic symptoms of diabetes led to the first medical consultation and the discovery of the existence of diabetes mellitus. Other unequivocal symptoms of diabetes, however, accompanied or preceded the symptoms of peripheral nerve disease in every instance. We have not seen a patient where "diabetic" neuropathy actually preceded the appearance of diabetes mellitus.

Information available in the literature regarding the general diabetic background of patients developing an associated neuropathy is both scanty and conflicting. Woltman and Wilder (15) state that this type of neuritic disease occurs commonly in well nourished diabetics who are free from acidosis and glycosuria. Wendt and Peck (16) found neuritic symptoms worse with hyperglycemia and with uncontrolled diabetes. In many individual case reports there is reference to gross neglect of both diabetic symptoms and diabetic treatment of years duration preceding the development of neuropathy. Similar diabetic neglect has been reported in groups of patients developing grave neuritic complications such as paralysis (Root and Rogers, 17) and neuropathic joints (Bailey and Root, 18). Joslin and Root (34) state that the symptoms of diabetic neuropathy always start during a time of uncontrolled diabetes, but why only some of the many diabetics who have such episodes develop neuritic disease is left unanswered. In order to clarify somewhat the relation of diabetic neuropathy to the presumed parent disease diabetes we have given particular attention to the details of diabetic management in our patients during the period preceding the development of this complication.

It has been generally recognized that diabetic neuropathy tends to occur in patients with mild diabetes, many of whom have had neither diabetic acidosis nor coma, as well as in those with more severe diabetes. Eleven of our patients had been in diabetic coma. Seventeen had had diabetic acidosis, including in this group all patients with clinical symptoms of acidosis as well as those admitted to the hospital with a plasma CO_2 combining power of less than 45 volumes per hundred. Ketone bodies were known to have occurred in the urine of another 27 patients. The remaining 70 patients (56 per cent) had never been in coma, acidosis, or had ketonuria as far as could be ascertained even at the height of diabetic non-regulation.

While criteria for satisfactory diabetic control are still under discussion they are of particular importance in judging the adequacy of treatment in mild diabetes which with little or no attention may not lead to major difficulty for many years. When immediate complications are not often encountered, recommendations for treatment must be made largely on our knowledge of remote complications. Certain minimal standards of diabetic treatment in general have been proposed (Tolstoi and Weber, 19) whereby treatment however managed is considered satisfactory if the patient maintains a general level of health permitting ordinary activities including gainful occupation, the body weight is maintained at the optimal level, the urine remains free of ketones, and if the patient is relieved of the frank symptoms of unregulated diabetes, polyphagia, thirst, urinary frequency, and so forth. It will be apparent that few of our diabetics who developed neuropathy had received treatment meeting even these minimal standards and that the period of neglect had extended over a period of many months or years.

None of this group was found to be among those regularly attending our diabetic clinic or under the adequate supervision of competent physicians with provision made for enlightened dietary management, frequent urinalyses, blood

sugar determinations when indicated, and check-up visits. In 25 cases there had been no diabetic treatment at all before the hospital admission. Of the remaining patients that had had some treatment nearly every one (98 cases) had had what could only be called "poor" care partly because of the obvious likelihood of failure. In this group were patients following vague qualitative diets having been advised to "cut out sweets", some who had adopted treatment plans prescribed for diabetic relatives, and some who had made only nonsensical modifications of their diet. Others had refused to accept insulin when recommended, and purchased alleged substitutes to be taken orally, or had sought advice from cultists. In some cases physicians attempted to make insulin administration solely an office procedure. Non-cooperative individuals, some too poor to purchase the necessary food and insulin even when medical advice was without cost, and some patients too stupid to learn the rudiments of their own care were all represented. In several instances patients alternately abandoned and resumed prescribed diet and insulin regimens as their health improved or deteriorated. Many patients encountered complications after abandoning well designed programs of treatment which, although giving excellent clinical results, had grown irksome. At least 22 patients were aware of constant heavy glycosuria, and 5 others noted heavy glycosuria recurring with every infection. Weakness, susceptibility to infections, or thirst and increased appetite, and so forth, were characteristically present intermittently or in some cases constantly as recorded in the individual case histories.

Objective evidence of the lack of adequate diabetic care in patients developing diabetic neuropathy was seen in the nearly universal loss of considerable weight, not due to dietary restriction but usually with excessive food consumption, immediately before or during the period of the development of the neuritic symptoms. While in 7 cases an unknown amount of weight had been lost and in 5 definite information was not recorded, 94 of the 125 patients (75 per cent) lost over 20 pounds of weight, 65 (52 per cent) over 30 pounds, and 40 (32 per cent) over 40 pounds. Seven patients lost between 100 and 130 pounds, having been very obese earlier and in some cases being still overweight in spite of the loss. In the young diabetics failure to gain weight normally or an actual loss was the rule. Fluctuation of the weight within a range of some 10-15 pounds coincident with infections or other factors influencing the diabetic status was commonly noted.

Enlargement of the liver has been observed frequently in poorly regulated diabetics, especially children (Pavy, 4, White, 20, Mauriac, 21, Hanssen, 22, Marble et al., 23 and White et al., 21). There is general agreement that the hepatomegaly disappears with effective treatment of the diabetes, in which protamine zinc insulin is of especial value among the juvenile group. Marble et al. found the incidence of other diabetic complications especially high among the patients with hepatomegaly, 7 of their 60 young diabetics, for example, having peripheral neuritis. In adults with diabetes there are fewer recorded observations regarding hepatomegaly but under the same circumstances it appears not uncommonly. Among our group with diabetic neuropathy excluding

those with cardiac, biliary tract, and other recognized hepatic disease, there were 38 in whom the liver was easily palpable. In 24 of these the liver was considered definitely enlarged. Observations regarding response to treatment of the diabetes were not complete but in 10 patients the liver was noted to reduce in size, not always to completely normal, however, with treatment of the diabetes.

The symptoms of diabetic neuropathy resembling in many respects those associated with other types of neuropathy (Brain, 25, Wilson, 12) have been described many times (Pavy, 4, Althaus, 3, Auchè, 8, Buzzard, 9, Williamson, 26, Woltman and Wilder, 15, Root, 27, Root and Rogers, 17, Jordan, 11, and others) but are distinctive enough to assist materially in differential diagnosis. Among our patients muscular cramps and aching were frequently early symptoms and muscular weakness especially of the legs was almost uniformly present. The extreme degree of this weakness is illustrated by 4 of our patients who for weeks were able to go upstairs at home only by crawling on hands and knees. In 2 other patients muscular "exhaustion" would follow walking a few feet to the bathroom. In another patient whose severe neuropathy developed acutely one week following diabetic coma there was a complete flaccid paralysis, bilateral wrist and foot drop, with the patient being able to do little or nothing for herself for 3-4 months before slow improvement began. Muscle tenderness aggravated by use and exertion was present in one-third of the cases and often persisted for months even after treatment was begun. Numbness, tingling, and paresthesiae such as "cold" feelings, aching and burning pains, and so forth, were usually prominent among the patient's complaints. Severe "shooting pains" both in deep and in superficial tissues were noted in more than one-fourth of the patients. The cramps, aches, and pains were characteristically worse upon exposure to cold and at night. The touch of bedclothes was often unbearable, sleep and rest impossible. Morphine and codeine were frequently necessary over periods of weeks or months to relieve pain. Patients so afflicted often became mentally depressed and emotionally unstable after a time, but usually not out of proportion to the discomfort experienced. Although a true psychosis was not encountered some physicians unfamiliar with this clinical entity, particularly the long duration of the symptoms and slow response to therapy, recommended psychiatric care or even committment to state institutions. Peripheral areas of anesthesia and unsteadiness of gait were less common symptoms. Foot drop was noted by a few ambulatory diabetics and once occurred practically as an isolated symptom. The lower extremities were affected more severely almost without exception. With distal involvement of the extremities the peroneal nerve was more vulnerable than the tibial, the ulnar more vulnerable than the radial or median. Occasionally symptoms occurred predominantly in the pudendal, femoral, or intercostal nerve areas, or asymmetrical areas in the extremities. This asymmetry, occurring also in alcoholic neuropathy, has been noted in diabetics by Pavy (4), Buzzard (9), Althaus (28), Harris (29), and others. Symptoms referable to disturbed function of the autonomic nerves, gastrointestinal tract and bladder will be discussed subsequently.

The symptoms of diabetic neuropathy were frequently intermittent or recur-

rent with gradual increase in intensity over a long period of time before assuming serious proportions. Many patients noted symptomatic exacerbation with or following sore throats, infections, relapses in diabetic management, and in some cases after the start of treatment. With uncontrolled diabetes, however, the tendency was toward increasing severity and persistence of symptoms. In patients with chronically poorly treated diabetes, with or without recurrent neuritic symptoms, a number of accidents all noted for their aggravating effect on the underlying disease were observed to precipitate acute and severe neuropathy. Brain (25) has seen diabetic neuropathy follow pneumonia, Jordan following diabetic coma (11) and diabetic acidosis (30), and Joslin and Root (34) following diabetic precoma. Events which seemed to produce or precipitate neuritic changes in our group of diabetics were severe upper respiratory infections (2 cases), "influenza" (4 cases), pneumonia (1 case), pyogenic infections (4 cases), toxic hyperthyroidism (2 cases), diabetic acidosis (4 cases), diabetic coma (6 cases), and surgical operations (4 cases). The relevant data in one of the latter cases are as follows:

J. H., #502333. This 37 year old laborer had had diabetes for 11 years. By following a qualitative diet avoiding high carbohydrate food and taking 20 units of regular insulin twice daily, he maintained his weight, felt well, and worked steadily. Urinalysis usually gave green to yellow tests with Benedict's reagent.

On January 28, 1942, abdominal pain, anorexia, and a slight fever appeared. A few hours later he became nauseated and vomited his food. Insulin was discontinued. When the symptoms had persisted for 2½ days his physician was called and a diagnosis of acute appendicitis made. He was taken to the local hospital where an acutely inflamed appendix was removed under ether anesthesia. A preoperative urine specimen showed a "2 plus" reaction for sugar. On the third postoperative day while still on a clear liquid diet polydipsia and polyuria appeared and led to the discovery of a heavy glycosuria and hyperglycemia. Only then was insulin resumed. His weight fell 10 pounds during the operative period. The daily insulin requirement for several weeks thereafter ranged between 85 and 125 units.

On the 7th postoperative day his hands and arms began to burn and feel numb. Shooting pains, tender muscles, joint pain and stiffness, severe constipation requiring the constant use of enemas, and complete impotence developed during the following 2-3 weeks. The symptoms increased in severity for 3-4 months and only after 6 months began to slowly improve. Two and one-half months after the onset he was referred to the University Hospital where in addition to the neurologic evidence of severe peripheral neuropathy, a high spinal fluid protein (Table II), stiff, painful joints, and moderately extensive retinal hemorrhages with exudates were found. His progress was followed closely for 20 months during which time it was necessary for him to spend 18 weeks in the hospital. At the end of this time although there was some limitation in joint movement and many neurologic residuals he was able to return to light work. The retinal hemorrhages had largely disappeared although slight retinal scarring and refractile exudates remained.

The neurologic examination of diabetic patients who have definite and persistent neuritic symptoms, excluding those with transient symptoms accompanying acute diabetic non-regulation to be discussed separately, seldom fails to elicit evidence of organic disease of the peripheral nerves proportional to the intensity and distribution of symptoms. Occasionally organic changes will be present when symptoms are minimal or will be recalled only by direct ques-

tioning. In our patients diminished or absent tendon reflexes was the commonest neurologic abnormality. The Achilles tendon reflexes were found to be absent in 101 patients (81 per cent) and greatly diminished in another 15. The patellar reflexes were absent on one or both sides in 70 cases (56 per cent) and greatly diminished in 29 more. Diminished or absent biceps and triceps reflexes were found in one-third of the cases. In several cases there was complete areflexia. The cutaneous sensibilities were blunted peripherally in about half of the patients. In this group areas of hyperesthesia and plantar dyesthesia were commonly found, and in 9 patients areas of complete anesthesia occurred. Pronounced muscle tenderness was present in 46 cases (36.8 per cent). Deep pain sensibility was usually unaltered except in patients with excessive muscle tenderness in whom increased sensibility was the rule. The vibratory sense at the ankles was diminished in 37 patients, and absent in 20. In 7 patients the vibratory sense was lost below the pelvis. Complete foot drop was present in 10 cases. The plantar responses were always in the direction of flexion, and clonus, exaggerated tendon reflexes, and spasticity was never encountered. There were no abnormalities of the cranial nerves except as evidenced by abnormal pupillary reflexes which were present in one-fourth of the patients. The abnormal pupils were in most instances miotic, reacting sluggishly to light, better on accommodation. Irregular and unequal pupils were observed. Two patients in whom there was neither evidence nor suspicion of syphilis had Argyll Robertson pupils. One patient had paradoxical pupillary reactions, similar in all respects to the Argyll Robertson type except that there was a distinct pupillary dilatation to light. Sluggish light reactions were noted to return to normal with general neurologic improvement.

The most reliable single sign of diabetic peripheral nerve disease, as in that associated with vitamin B deficiencies (Aring et al. 31), is diminished or absent tendon reflexes. In some early cases with pronounced muscle tenderness the tendon reflexes may show increased activity for a time. While diagnoses based on subjective sensory tests are often regarded suspiciously, careful and repeated examinations in the great majority of our patients have given very uniform results if too much reliance on minimal deviations is avoided. It is significant that there was no clinical evidence of primary spinal cord disease or involvement of the lateral and anterior funiculi in these cases. Such changes have frequently been thought to occur in diabetic neuropathy (Woltman and Heck, 32) but good clinical and pathologic evidence is lacking (Woltman and Wilder, 15). Although pathologic observations in our patients will not be reported at this time, the symptoms and signs are those of peripheral nerve involvement with perhaps secondary degeneration of the fasciculi propriae and posterior columns of the spinal cord which in severe cases would appear to be anatomically inescapable. The spinal fluid changes to be discussed shortly are indicative of pathologic changes in the spinal nerve roots and perhaps of the associated tracts in the spinal cord. Abnormal pupillary reactions—miotic pupils reacting sluggishly to light but better on accommodation—have been observed in patients with diabetic neuropathy by many authors including Leyden (7), Major (157), and Jordan (11). Five of Jordan's patients had Argyll Robertson pupils in the

absence of any indication of syphilis. Waite and Beetham (33) observed pupillary abnormalities in patients with diabetic retinopathy especially those with hemorrhagic and proliferating changes. Ten of their patients had Argyll Robertson pupils in 5 of whom there was neither evidence nor suspicion of syphilis.

Spinal Fluid. A definite abnormality in the spinal fluid of patients with uncomplicated diabetic neuropathy in the form of increased total protein has been found by a number of investigators although this occurrence is not widely known. Root and Rogers (17) among 11 patients with paralysis reported 4 spinal fluids with total proteins of 95, 88, 80, and 55 mg. per hundred cc. Jordan (11) among 40 patients with neuritic manifestations whose spinal fluids were examined found the total protein above 50 mg. in 22 cases, and above 60 mg. per hundred cc. in 15 cases. Joslin and Root (34) reported the findings in a large number of diabetic patients to which further observations were subsequently added (Root, 35). Of 84 patients with diabetic neuropathy, 29 per cent had total protein values between 51 and 40 mg. per hundred cc., 44 per cent between 71 and 120 mg., and 14 per cent between 121 and 390 mg. per hundred cc. Of 53 diabetics with surgical infections of the feet, who were presumably without clinical evidence of diabetic neuropathy although this point is not entirely clear, 26 had total protein values between 51 and 70 mg. per hundred cc. and 17 between 71 and 120 mg. per hundred cc. Merritt and Fremont-Smith (36), Angle (37), Rudy and Muellner (56), and Needles (139) have reported similar findings in a few cases. The height to which the total protein may rise is to be emphasized for occasionally there may be clinical confusion (38) with the entirely different Gullian-Barré syndrome of polyradiculoneuritis (Garvey, et al, 39, DeJong, 40, Roseman and Aring, 41, Baker, 42, and others).

The spinal fluid was not routinely examined in our group of patients, usually only when the diagnosis was not entirely clear. Thirty-nine examinations were made in 31 patients. Ten fluids were normal. Thirteen had excess total protein ranging from 48 to 80 mg. per hundred cc. The detailed findings in the remaining cases are given in Table II. The high values of 268, 364, and 426 mg. of total protein per hundred cc. were encountered in patients with severe neuropathy in whom there was not the slightest doubt as to the correctness of the diagnosis. The patient with the highest value, 426 mg. (G. G., #502930) had a value of 114 mg. per hundred cc. five weeks earlier, near the onset of the neuritic symptoms, and in the interim in spite of treatment had become greatly worse. Later there developed arterial hypertension, retinal hemorrhages and exudates, and finally proliferating retinopathy with retinal detachment. He died in the hospital 9 months after the onset of the neuropathy of an acute coronary occlusion. The persistence of the elevated total protein for several months was noted in 2 patients during a slow convalescence. The cellular content, pressure, and spinal fluid dynamics were always normal, and the globulin uniformly increased. Although patients with severe neuropathy were found among those with normal spinal fluids, only those with severe neuropathy had the highest values for total protein. As far as our data go, the spinal fluid changes offer little additional basis for prognosis in individual cases.

Gastro-intestinal Disfunction. Among an average group of diabetics receiving

modern treatment, gastro-intestinal disturbances are probably no more frequent than among a similar group of non-diabetics. Striking abnormalities, however, in the form of severe constipation, chronic diarrhea, anorexia and nausea often accompany the development of diabetic neuropathy. Eliminating from con-

TABLE II
Spinal Fluid Findings in Diabetic Neuropathy

CASE	CELLS	PANDY	PROTEIN <small>mg./100 cc.</small>	COLLOIDAL GOLD	MASTIC	GLOBULIN	SEROLOGY	
							Blood	Sp. fl.
5 cases	0-2	0-+	48-60	0000000000	000000	0-++++	1 pos.	Neg.
8 cases	0-6 lymphs	0-+	62-80	0000000000 to 0011000000	000000 to 222100	+ - + + + +	Neg.	Neg.
D. S., #391721	0	+	69	4333210000	333210	++++	Neg.	Neg.
#403008	3 lymphs	+	364	0000121100	112321	++++	Neg.	Neg.
#406577	5 lymphs	++	98	0011100000	221100	++++	Neg.	Neg.
#418504	3 lymphs	+++	121	0001210000	121000	++++	Neg.	Neg.
#462378	5 lymphs	++	133	0012210000	222210	++++	Neg.	Neg.
#480808	4 lymphs	+++	133	0001100000	222210	++++	Neg.	Neg.
#482133	3 lymphs	++	105	0012100000	122210	++++	Neg.	Neg.
#492561	2 lymphs	Neg.	83	0000000000	110000	+++	Neg.	Neg.
J. II., #502333	6 lymphs 6 lymphs 3	++ ++	268 167 148	0001100000 0001110000 0000000000	233322 011000 222210	++++ ++++ ++++	Neg. Neg. Neg.	Neg. (4-16-42) Neg. (7- 9-42) Neg. (12-15-42)
G. G., #502930	1 lymph 7 lymphs	+++ ++++	114 426	0001100000 0012221000	233321 133332	++++ ++++	Neg. Neg.	Neg. (6-15-42) Neg. (7-20-42)
W. H., #506775	0 2 lymphs	Neg. +	129 118 118	0000000000 0011100000 0011100000	022221 012221 222221	++ ++++ ++++	Neg. Neg. Neg.	Neg. (7- 6-42) Neg. (8-20-42) Neg. (3-23-43)

sideration symptoms due to other possible gastro-intestinal diseases by the customary diagnostic measures of roentgen examination, sigmoidoscopy, stool examination, etc., 76 (61.8 per cent) of our 125 patients had such symptoms. The most common abnormality, constipation, which it has been stated is not more common among diabetics than among non-diabetics (Marble, 35) developed as

a change in bowel habit with the development of neuritic symptoms in 53 patients. In 22 of these the condition was refractory enough to require the persistent use of enemas to assure bowel movements oftener than every 4-6 days and prevent fecal impaction.

In 27 patients types of chronic diarrhea with 4-6 or more liquid stools daily appeared, in many cases alternating with or following a period of severe constipation. In 11 patients 2-4 days of diarrhea would usually alternate with 1-2 weeks of severe constipation. Six patients noted recurrent periods of diarrhea lasting weeks or months, and 10 patients had almost continuous diarrhea. In some patients the diarrhea was nocturnal with liquid stools being passed all night long at regular 20 min. to 2 hr. intervals with the penalty for sound sleep being fecal incontinence. In others, each meal would be followed by gaseous distension, borborygmi, and the urgent passage of 2-4 stools containing particles of recently eaten food. While the stools were usually liquid, light in color and foul smelling, bloody stools were noted by 7 patients. One patient died in the hospital of a diffuse exsanguinating gastro-intestinal hemorrhage one week after severe diabetic acidosis was treated. ✓ Stool examinations in the hospital failed to reveal excess fat, undigested meat fibers, ova or parasites. Patients with severe constipation or chronic diarrhea were observed to have recurrent periods of nausea and vomiting (H. C., #524359, p. 116, and W. G., #492561, p. 118) once with pain comparable to that of the gastric crisis of tabes (T. F., #519430, p. 119).

While the clinical evidence of grossly disturbed gastro-intestinal motility in these cases is indisputable it has been difficult roentgenologically to demonstrate positive findings other than the absence of common pathologic entities. Special ✓ study of small intestinal motility was undertaken in several patients. One patient with chronic nocturnal diarrhea showed abnormally rapid intestinal motility. Four patients, one already referred to in detail above (H. C., #524359), who in addition to chronic diarrhea, or alternating severe constipation and diarrhea, had pronounced anorexia with nausea much of the time showed abnormal gastric retention, once for 24 hours, or unusually slow progress of the barium meal through the small intestine with wide scattering and puddling in the intestinal loops. A detailed study to compare these findings with the altered mucosal pattern and other roentgenologic abnormalities reported to occur in idiopathic steatorrhea (Snell and Camp, 43), vitamin deficiencies (Mackie, 44, Golden, 45, Sussman, 46), and the celiac syndrome (Farber, 47) has been undertaken (48).

A "diabetic diarrhea" has received scattered comment for many years. Bowen and Aaron (49) associated achlorhydria with the diarrhea of 10 diabetics. All of their patients were emaciated, 2 had evidence of neuritic disease mentioned, and 1 with a "cord bladder" was shown at autopsy to have posterior column degeneration. Bargaen, Bollman, and Kepler (50) compared the diarrhea of diabetics with the steatorrhea of pancreatic insufficiency and found that only the latter condition responded to the oral administration of pancreatic extracts. Marble (35) described diarrhea as a "grave as well as a distressing complication"

of diabetes and suggested the possibility of a neurogenic origin. White (51) noted that "nocturnal" diarrhea was frequently an accompaniment of neuritis in young diabetics. The Boston observers believe that liver therapy is of benefit in this condition. Our data serve to emphasize that disturbed gastro-intestinal function is a common accompaniment of diabetic neuropathy and one that, in view of the other evidence of disturbed autonomic nerve function, as well as the high incidence in the same patients of genitourinary and sphincter abnormalities to be cited, should be considered as resulting from autonomic nerve disease. Two patients with these symptoms who died were reported pathologically to have degenerative changes in the nerve trunks of the esophageal plexus and about the celiac ganglia. There is no clinical evidence to suggest that neuropathy follows diarrhea in sequence, as in some of the deficiency diseases, although the presence of diarrhea and even more the occasionally associated anorexia and nausea makes the diabetic status exceedingly difficult to control.

Genitourinary and Sphincter Disturbances. Disturbed genitourinary function and impaired sphincter control have been considered rare complications of diabetes. Until recently only occasional reports (53) of unexplained bladder "paralysis" or the so-called diabetic "cord-bladder" were made without detailed investigation or recognition of the relation to diabetic neuropathy. McKittrick and Root (52) reported 3 diabetic patients with chronically distended, paralyzed bladders in whom no generalized or local cause was found. Jordan and Crabtree (53) reported 7 patients with distended bladders and large urinary residuals. At least 6 of the patients had neuritic symptoms and evidence of organic nerve disease, and the authors attributed the bladder paralysis to diabetic neuropathy. The following year Jordan (11) added 5 additional cases. The prognosis was noted to be poor since many of the patients died a few months or years after the onset and in none of them did the bladder function return to normal. Gill (54) reported 2 cases of diabetic "cord" bladders, both with neuropathy and 1 with diabetic retinal lesions, who died shortly of urinary tract infections. Baldwin and Root (55) discussed the relation of bladder paralysis to urinary tract infections in diabetics and the treatment of both. In another communication (35) they expressed the opinion that the bladder paralysis of diabetics could be compared to that following traumatic injury of the spinal cord. Rudy and Muellner (56) reported a detailed study of 11 patients having diabetic bladder paralysees in 10 of whom there was evidence of neuritic disease elsewhere. Repeated cystometric examinations were made and they were able to show gradual improvement during the course of treatment.

Among our 125 patients with diabetic neuropathy 32 (25.6 per cent) had genitourinary and sphincter disturbances. Complete lack of sexual potency was recorded as a complaint in 19 patients (27.5 per cent of all males) and this often preceded any other symptom of peripheral nerve disorder. Urinary incontinence was a complaint of 10 patients. Five of these and 2 others, also, had fecal incontinence. Difficulty in urination, hesitancy, a slow, weak stream, or acute urinary retention were symptoms leading to the discovery of an atonic type of bladder paralysis in 18 patients, 15 of them males. Thirteen of these had cysto-

metric examinations which invariably showed impaired or absent sense of filling, very low expulsive force, and an increased bladder capacity. Hot and cold sensibilities were occasionally impaired or lost. The residual urine varied from nothing to over 300 cc. Uninhibited bladder contractions did not occur. Special investigations including sounding and panendoscopy were carried out routinely in order that vesical neck and urethral obstructions might not be overlooked before concluding that the atonic bladder paralysis was neurogenic in origin. Fifteen of the 18 patients with bladder paralysis had in addition impotence or defective sphincter control. Two patients with atonic bladders had impotence and both urinary and fecal incontinence. Of the 32 patients with genitourinary and sphincter disturbances, 25 (78 per cent) had either severe chronic constipation developing with the neuropathy (12 cases) or some type of chronic diarrhea (13 cases).

The sphincter disturbances we have described result almost certainly from disease of the pudendal nerves. Two patients with atonic bladders had exquisite cutaneous hyperesthesia in the pudendal area, severe enough in one case to lead to nerve section. The bladder paralysis of diabetic neuropathy is properly classified as an atonic neurogenic paralysis (Nesbit and Gordon, 57) such as occurs in *tabes dorsalis*, pernicious anemia with peripheral nerve and posterior column disease, and alcoholic neuropathy (Langworthy, Kolb and Lewis, 58). Dees and Langworthy (59) produced this type of bladder disturbance experimentally in cats by sectioning the posterior sacral nerve roots. It is of interest in relation to the gastro-intestinal symptoms already discussed that severe obstipation resulted from this operation, also. In our diabetics an impaired or absent sense of bladder filling was the only constant sensory defect found by cystometric examination. Whether the bladder syndrome is wholly sensory in origin or whether there is decreased motor (parasympathetic) activity, too, is difficult to determine. Emmett and Beare (60) have emphasized the difficulty in analyzing the clinical phenomena in terms of primary sensory defect, primary motor atony, either or both of these complicated by vesical neck obstruction, and finally the factor of infectious or mechanical injury to the detrusor muscle. Learmouth (61) has shown that faradic stimulation of the lumbar sympathetic trunks in the human being produces emptying of the seminal vesicles and expulsion of the prostatic secretions into the posterior urethra. Both he and Allen and Adson (62) have found that loss of ejaculation may follow sympathectomies in male patients. An analogous deficiency was seen in one of our diabetic patients who had recovered 18 years previously from an evidently severe diabetic neuropathy. In this patient complete absence of ejaculation followed the acute episode although nearly normal erections were possible. Examination showed dependent rubor of the feet which subsided with elevation of the legs, an abnormal orthostatic fall in blood pressure, and diminished sweating below the knees with absent sweating over the hands and feet. Cystometric examination showed a bladder capacity of over 650 cc., first desire to void at 475 cc., residual urine 150 cc., and sense of filling absent but sense of hot and cold present. Residual sympathetic nerve degeneration was thought to account for the loss of ejacu-

latory power. The almost invariable association of complete impotence with atonic bladder paralysis in males, in only 1 case was normal function retained, is evidence that impotence in patients with diabetic neuropathy is likely to be a symptom of organic nerve disease.

The early recognition of bladder atony is extremely important for the presence of residual urine interferes with fractional collections of urine, urinary infections which frequently supervene may make good diabetic regulation impossible, and long standing vesical distension particularly with infection may produce permanent bladder damage. If recognized early and treated well the condition may remain entirely benign. We have seen in 1 case a completely atonic bladder requiring suprapubic cystotomy return to normal, functionally and cystometrically, in 1 year's time, as a part of the general neurologic improvement. The principles of urologic treatment have been summarized by Nesbit and Gordon (57) and are directed mainly toward preventing residual urine and chronic urinary tract infection. Periodic evacuation of the bladder every 3-4 hours assisted by standing, straining and Credé are generally adequate in treatment. Patients with orthostatic hypotension who generally have atonic bladders are urged to void regularly at night, also. Vesical neck obstructions must be meticulously avoided. Only one of our patients required suprapubic cystotomy and in him bladder function eventually returned to normal. No other serious complications have as yet been encountered.

Peripheral Autonomic Nerve Disease. The participation of the autonomic components of the peripheral nerves in different types of neuropathy has been recognized in scattered instances (Guttmann, 63, Wilkins and Kolb, 64, Shumaker, 65, and others). Patients with diabetic neuropathy may develop unusual degrees of peripheral sympathetic nerve damage as revealed by sweating deficiencies, loss of vasomotor and pilomotor control, dependent edema, and certain types of skin alteration. Since most of the information in this regard was uncovered in the 35 patients in this series studied personally, the true incidence is probably higher than the figures we can give indicate. Excluding patients with cardiac disease, nephritis, low serum proteins, varicose veins, etc., there were 26 patients who had dependent edema of the lower extremities appearing during the course of the neuropathy. In several instances pitting edema as high as the knees was observed. This type of edema occurring as it does in many different types of peripheral neuropathy is presumably due to involvement of the vasomotor nerves (Pryce, 6, Buzzard, 9). Lange (66) reported observations showing that capillary permeability is increased after sympathectomy. Thirteen patients noted decreased or absent sweating over the feet and legs usually in areas of sensory disturbance. Objective confirmation of this abnormality was made in 11 patients by the use of the starch-iodine sweating test (Minor, 67, List and Peet, 68). Three patients had localized areas of painful hyperesthesia in which there occurred profuse sweating at times when the skin elsewhere was dry. Intolerance to extremes of temperature, both hot and cold, was a complaint not infrequently encountered in these patients. Drenching night sweats were noted by 6 patients who were afebrile and who were demon-

strated by careful investigation to be free of infection or evidence of tuberculosis. These observations suggest impaired temperature regulating mechanisms perhaps due to imperfect control of the sweat glands and vasomotor adjustment of cutaneous blood flow to be referred to in detail below. In 4 of our recent patients with chronic neuropathy the skin over the extremities became shiny and atrophic, and, in another patient, dry and fissured apparently due to decreased function of the sebaceous glands. Loss of vasomotor and pilomotor control, and dependent rubor of the extremities not indicative of peripheral vascular disease was observed during skin temperature studies to be described below. The following case reported in detail by Foster (170) illustrates some of the effects of peripheral degeneration of autonomic nerves in a patient with an unusual, "neurotropic" (Jordan, 11, 30; Bailey and Root, 18) type of joint destruction.

W. E., #519963. This 23 year old white male entered the hospital complaining of trouble in walking, dependent edema and enlargement of the left foot. He had had diabetes for over 8 years treated by a haphazard diet and small daily injections of regular insulin. He had not gained in weight or height after the onset of the diabetes and had never been strong, but had been able to earn a living managing a pool room.

Two to three years before admission his legs gradually became numb as well as weak. Six months before admission the left foot became enlarged, the arch flattened, and edema was noted to appear with standing. There was slight pain on walking especially after the foot became edematous.

Physical examination showed a generally weak but fairly well developed and well nourished young male. The left pupil was larger than the right and both reacted sluggishly to light and accommodation. Numerous punctate hemorrhages and scattered areas of exudate were present in the retinae. The tendon reflexes were all absent even with strong reinforcement. The dorsiflexors of the left ankle were disproportionately weak. Pain, tactile, and temperature sensibilities were absent below both knees but were about normal above the mid-thigh region. There was diffuse swelling about the left foot and ankle but no break in the skin or apparent infection. The feet were warm and the arterial pulses bounding. X-ray films of the left foot showed extensive disruption of the tarso-metatarsal joints with loss of joint surfaces and many loose bodies.

The blood pressure on many occasions averaged in the supine position 120/70 mm. of mercury with a pulse of 65 per minute. In the erect position the blood pressure gradually dropped to 100/60 or below with the pulse rising to 110-120. A starch-iodine sweating test showed no sweating below the knees. Cystoscopy showed no evidence of filling, but no urinary residual. Skin temperature studies (Dr. D. B. Foster) showed the left leg to be constantly warmer than the right with slight local heat in addition about the left foot. Nicotine produced a fall in skin temperature in both arms and in the right leg but a rise in the temperature below the left knee.

The diabetes was found to be poorly controlled with continual hyperglycemia but without ketonuria or acidosis. After 2 months application of a leg cast all pain and local heat had disappeared from the affected foot. There was, however, no change in the roentgen appearance of the bones of the foot.

Orthostatic Hypotension and Orthostatic Tachycardia. Defective orthostatic regulation of the blood pressure was a somewhat unexpected finding in 8 of our patients with diabetic neuropathy (69). This physiologic abnormality has been reported in severe form in less than a hundred cases since it was first described by Bradbury and Eggleston in 1926 (70). The characteristic symptoms are

faintness or syncope when the subject assumes an erect position, especially after arising in the morning, when fatigued, or after exertion such as climbing steps. The blood pressure in the supine position is usually normal but the systolic and to a lesser extent the diastolic pressure declines precipitously on standing. When the systolic pressure falls below 50–60 mm. of mercury faintness, dizziness, or syncope follows. The syndrome, although no uniform clinical entity, is often associated with disturbed function of the sympathetic nervous system (Baker, 71, Stead and Ebert, 72, Young, 73, Jeffers et al., 74, Laplace, 75, and others). In the previously reported cases, to which extensive reference has recently been made by Spingarn and Hitzig (76), the circulatory abnormality has been associated with tabes dorsalis, unclassified diseases of the central nervous system, sequellae of encephalitis (Alvarez and Roth, 77, Laufer, 78, Masee, 79), myasthenia gravis, and Addison's disease. In a large number of cases, however, the etiology has been obscure. The syndrome has not been reported to occur with the commoner types of peripheral nerve disease nor in diabetic neuropathy, with the possible exception of Ellis and Haynes' (80) second case in which diabetes was present but with little to suggest typical neurologic disease due to diabetes.

Orthostatic hypotension with typical symptoms of orthostatic circulatory insufficiency occurred in 5 of our patients (Table III). None of them were confined to bed when the blood pressure readings were taken. When changing from the supine to the erect position the systolic blood pressure fell 50 or more mm. of mercury, the diastolic pressure often became imperceptible, and the pulse weak, rapid and of poor quality. Lack of reflex cardiac acceleration was not observed. The Flack test (81) was made in 3 patients and resulted in prompt syncope in each. Oliguria and diminished renal function with standing was demonstrated in the 1 patient tested.

Three patients without definite symptoms of orthostatic circulatory insufficiency had less pronounced but excessive fall in blood pressure with postural change and orthostatic tachycardia. 2 of these patients (T. F., # 519430, p. 119, and W. E., # 519963, p. 133) have already been presented in detail. The third was admitted to the hospital for investigation of arterial hypertension associated with diabetes. The unusual genitourinary symptoms and the evidence of sympathetic nerve degeneration have already been referred to (p. 131). His blood pressure when supine averaged 178/96 (pulse 102) and when standing 120/80 (pulse 120).

Aside from the uniform background of diabetic neglect and neuritic symptoms of fairly long duration this group had other notable abnormalities in common (Table III). Chronic or recurrent diarrhea was present in 5 cases, severe constipation in another. All of the males except 1 were impotent. Five had an atonic bladder paralysis and in 2 others suggestive symptoms were present but not investigated cystometrically. Six of the 8 had abnormal pupillary reactions. In 3 cases the pupils were of Argyll Robertson type, in 2 cases there being no evidence of syphilis while in the third there was a history of treated sero-positive primary lues. The majority had evidence of peripheral sympathetic nerve disease. Sweating was decreased to absent over the feet and lower legs in 6 patients.

TABLE III
Orthostatic Hypotension and Orthostatic Tachycardia in Patients with Diabetic Neuropathy

	PREVIOUS HISTORY	NEUROLOGIC STATUS	PUPILS	GENITO-URINARY	GASTRO-INTESTINAL	PERIPHERAL SYMPTOMATIC	CIRCULATORY SYMPTOMS	BLOOD PRESSURE, PULSE CHANGES
C. B. #392539 20, male	Diabetes 9 yrs. Uncooperative. Neuritic symptoms 3 yrs., progressive.	Hypalgnesia and analgesia below L. 1. Knee and ankle reflexes absent.	Unequal. Sluggish reaction to light.	Impotence. Distended, atonic bladder.	Chronic diarrhea. Food in stools 2 hrs. after eating.		Dizzy spells, syncope when standing.	130/65, supine. → 77 standing, with syncope in 3-4 min.
W. G. #492561 43, male	Diabetes 6 yrs. Abandoned treatment 4 yrs. Neuritic symptoms 1½ yrs.	Weak, sore muscles, hyperesthesia, tendon areflexia.	Argyll Robertson (no lucas).	Impotence. Poor sphincter control.	Chronic diarrhea, anorexia, vomiting.	Edema. Sweating decreased to absent over legs.	Dizzy spells, syncope with standing.	100/60 supine. 80/40, sitting. 50/3 standing, syncope in 2-3 min.
O. H. #161320 51, male	Diabetes 31 yrs. Barely survived, early. Neuritic symptoms 2-15 yrs.	Tender muscles, hypalgnesia, distal anesthesia, ankle reflexes absent.	Argyll Robertson (no lucas).	Impotence. Atonic bladder.	Chronic diarrhea, anorexia, vomiting.	Edema. Dry skin, dependent rubor.	Dizzy spells with lifting exertion, etc.	130/78 (p. 100) supine. 50/40 (p. 120) standing, blood pressure well maintained.
F. B. #431043 37, male	Diabetes 7 yrs. Crude treatment. Neuritic symptoms 6 mos.	Weakness, hyperesthesia, tendon reflexes sluggish.		Impotence.	Alternating diarrhea and constipation.		Dizzy spells, with standing and exertion.	120/90, supine. 70/60 → 60/50, with standing.
J. Q. #431358 19, female	Diabetes 5 yrs. Uncooperative. Neuritic symptoms 1 yr., onset after coma.	Weakness, burning pains, tender muscles. Tendon reflexes sluggish.	Sluggish reaction to light.	Hesitancy. Hypotonic bladder.	Constipation, diarrhea. Anorexia and nausea.	Edema, dry skin, sweating absent over lower legs.	Weakness, faintness when up and active.	130/90 (p. 110) supine. 70/7 → 90/70 (p. 150), standing, 60/40 (p. 160) after climbing stairs.
T. F. #519430 44, male	Diabetes 3 yrs. Poor treatment. Neuritic symptoms 1½ yrs.	Hyperesthesia, sore muscles, knee and ankle areflexia, ataxia.	Argyll Robertson (treated lucas).	Impotence. Atonic bladder.	Constipation. Epigastric pain, nausea, vomiting.	Edema, sweating defects, vasomotor paralysis.	Dizziness and headaches with standing.	104/60 (p. 80) supine. 80/50 (p. 120) standing (after salt deprivation).
W. E. #519553 23, male	Diabetes 8 yrs. Hazard treatment. Neuritic symptoms 2-3 yrs.	Distal hypalgnesia, anesthesia below knees. Tendon areflexia.	Unequal. Sluggish reaction to light.	Early atonic bladder.	None	Edema. Charcot joint, sweating defect, vasomotor paralysis.	None	120/70 (p. 65) supine. 100/60 (p. 110) standing.
G. R. #540554 49, male	Diabetes 24 yrs. Severe neuropathy early, recovered. Residual signs.	Patellar reflexes diminished, ankle reflexes absent.	Normal.	No ejaculation. Atonic bladder.	None	Sweating lost over lower legs, dependent rubor.	Admitted for investigation of arterial hypertension.	178/96 (p. 96) supine. 120/80 (p. 120) standing.

Skin temperature studies carried out in 2 cases showed loss of normal vasoconstriction in the lower extremities when exposed to a cold environment.

The occurrence of orthostatic hypotension and the closely related phenomenon orthostatic tachycardia in patients with diabetic neuropathy is of considerable interest both as a feature of diabetic neuropathy and as a source of further information regarding the pathogenesis of abnormal orthostatic blood pressure regulation. When the syndrome occurs in association with diabetic neuropathy the general clinical features are quite uniform. It has been observed by Barker (82) and Chew, Allen, and Barker (83) that patients with orthostatic hypotension of diverse etiologies exhibit clinical abnormalities not essentially related to the faulty control of blood circulation. The clinical findings almost invariably present, syncope, dizzy spells, weakness after exertion, impaired renal function with oliguria when upright, etc., are directly related to the circulatory collapse when the patient stands. Other conditions which are of sporadic occurrence, and therefore not necessarily related to the orthostatic maintenance of blood pressure, include lack of reflex cardiac acceleration (present in all three of Bradbury and Eggleston's cases), impaired regulation of the body temperature (symptoms worse during the summer's heat, generalized "cold" feeling, 77) regional or generalized sweating deficiency, chronic diarrhea, edema of the lower extremities, neurogenic bladder paralysis, and impotence. The latter symptoms, with the exception of lack of reflex cardiac acceleration, occurred commonly in our patients with severe diabetic neuropathy, even in those without orthostatic circulatory abnormality, and can largely be accounted for on the basis of disease of the peripheral autonomic nerves. This degeneration, moreover, appears to play an important etiologic rôle in the syndrome although the relative importance of several mechanisms, loss of adequate arterial vasoconstriction with increased hydrostatic pressure, decreased venous return to the heart (84) whatever the immediate cause of that may be, decreased blood volume when standing (84, 85), and perhaps loss of afferent nerve impulses normally initiating reflex orthostatic circulatory adjustments, is not yet known. In some of the reported cases central nervous lesions rather than peripheral nerve disease appear to be responsible. If the pupillary abnormalities present so often (71, 86, 87, 88) signify more than peripheral nerve disease, and it is thought that at least Argyll Robertson pupils do (89), the essential lesion of the orthostatic syndrome may possibly be in the hypothalamic region subserving autonomic functions.

Association of Diabetic Neuropathy and Retinopathy. The existence of a specific type of retinal disease caused by diabetes mellitus is no longer disputed (Wagener and Wilder, 90, Wagener, Story and Wilder, 91, Gray, 92, Waite and Beetham, 33, Barkan and Gray, 93, and others). In recent years, moreover, it has been shown to affect young diabetics as well as the old, those with severe diabetes as well as mild, and that it appears in the absence of hypertension, impaired renal function, and albuminuria (Hanum, 94, White, 35, O'Brien and Allen, 95, Bloch, 96, and Tooke and Nicholls, 97). The etiology of diabetic retinopathy, the factors both immediate and remote which are responsible and their relationship to diabetes, however, remains unsettled. Wagener, Story and

Wilder (91) pointed out that retinal disease and peripheral nerve disease were frequently associated together in diabetic patients, that 25 per cent of a large group of patients with diabetic retinitis had in addition diabetic neuritis. The converse relationship appears in our patients with diabetic neuropathy since 43 (34.4 per cent) of the 125 had retinal disease characteristic of that due to diabetes. The coincidence of these 2 diabetic complications appears more than fortuitous since the total incidence of neuritic disease in our diabetic clientele is around 5 per cent, and the incidence of diabetic retinal lesions probably not over 10 per cent. In a few cases we have seen the 2 complications developing simultaneously. The earliest stage of diabetic retinopathy, characterized by punctate hemorrhages located centrally and near the larger retinal blood vessels, was found in 16 of our patients. Hemorrhages with "cotton-wool" or refractile exudates occurred in another 24. In 3 patients we observed the retinal lesions progressing through these stages to that of a proliferating retinopathy, with linear and superficial hemorrhages, scar tissue, new-formed, dilated, tortuous veins and capillaries, etc. One of the latter patients was first seen when complaining of symptoms of a mild neuropathy 9 months after glycosuria had been discovered in a routine urinalysis. Four years later decreased visual acuity led to the discovery of punctate hemorrhages and exudates. In another 6 months an extensive proliferating retinopathy was present reducing her visual acuity beyond the point of serviceability. She had always been erratic in following recommendations for treatment of her mild diabetes but had encountered no other complications. A second patient, a 33 yr. old male, developed a severe neuropathy 3-4 weeks after we started treatment of the diabetes which he had flagrantly neglected for 5 years. A few weeks after the onset of neuritic symptoms punctate retinal hemorrhages appeared, followed in a few more weeks by extensive hemorrhage with exudates and, for the first time, arterial hypertension. The neuritic symptoms slowly improved during the following months but the visual status became increasingly grave. Nine months after the appearance of the first retinal lesions a proliferating retinopathy had developed, with retinal detachment, O. S., and almost complete loss of vision. The course was terminated by sudden death in the hospital by the occlusion of an atheromatous coronary artery. The third patient who had a most unusual recovery from this type of retinal disease has been referred to in detail above (D. S., #391721, p. 114). In a few other instances retinal hemorrhages were observed to disappear gradually as adequate diabetic treatment was maintained over a period of months.

The pathologic changes in diabetic retinopathy, well described by Hanum (94) in his excellent monograph, are essentially due to hemorrhages from small capillaries and veins of the retina. The proliferative aspect in severe cases is associated with connective tissue organization of areas damaged by hemorrhage. Hanum's statement that he "never found any relationship between arteriosclerotic vascular changes and the gravity of the retinal changes" is in agreement with the experience of others (33, 91). There is thus little support for the opinion sometimes expressed (Anderson, 98) that the retinal lesions are analogous to the arteriosclerosis of diabetes or that a fundamental abnormality of fat

tients presented clinical evidence possibly indicating significant degrees of occlusive vascular disease while in 100 (80%) there was none.

Skin temperature determinations under standard conditions have proved to be a valuable technique in the quantitative estimation of peripheral blood flow. In order that vascular disease not ordinarily detected clinically might not be overlooked in our patients with diabetic neuropathy skin temperature studies were done in 8 selected cases.

One of the important temperature regulating mechanisms of the body concerns the vasomotor control of the cutaneous and subcutaneous blood vessels. Heat is dissipated more rapidly when the surface temperature rises (vasodilation) and conserved when the surface temperature falls (vasoconstriction). If an average, healthy, unclothed or lightly clothed individual under basal conditions is exposed to an environmental temperature of 30–32°C. over a period of time adequate for acclimatization, the skin temperature in various regions of the body will be found approximately uniform, some 2–3°C. below the rectal temperature (112, 113, 114). As the environmental temperature falls the need for heat conservation will arise and vasoconstriction of the cutaneous blood vessels will occur, and result in diminished surface blood flow and a lower skin temperature. The latter does not fall uniformly in all areas of the body, however, but to a disproportionate extent in the extremities (115, 116). Vasoconstriction begins in the lower extremities when the room temperature is about 29°C. and is complete at about 27°C. when the temperature over the feet is 5–6°C. lower than the average trunk temperature (a difference of 10°C. or so may be seen in Raynaud's disease). Vasoconstriction in the hands begins at about 26–27°C. and progresses to a similar degree. The average trunk temperature falls but 1–2°C. as the environmental temperature falls from 30°C. to 24°C. and the internal temperature not at all.

For clinical testing it is sufficient to compare the internal or the average trunk temperature with that of the distal extremities at the extremes of the zone of vasomotor control (25°–30°C.). The factor of humidity may be neglected (117). A subnormal temperature of the extremities after exposure to an environment of 30–32°C. is characteristic of occlusive arterial disease (occasionally abnormal vasoconstriction). Failure of the peripheral skin temperatures to fall with exposure to a room temperature of 25°C., with chilling of the patient, indicates defective vasomotor function, etc.

Hospitalized patients were used for all tests. At 7 a.m. without preceding food, water or activity they were transferred to a stretcher and taken to a still room where the temperature had previously been adjusted to the desired level. There they were exposed to the air for 1 hour, or longer if the skin temperatures were not constant, wearing the minimum of clothing. Selected spots (115) over the trunk, hands and feet were chosen for recording the skin temperatures with a Tycos Dermatherm. Of particular interest is the comparison of the average trunk temperature (average of the forehead and infraclavicular readings) with the average foot temperature (average of the plantar surfaces of the first three toes, mid-plantar, and mid-dorsum readings) under different environmental conditions. Data from 4 typical cases is presented graphically (Fig. 1).

M. G., #521512. The detailed case history of this patient has been presented above (p. 127). She was chosen for skin temperature studies because of her complaint of "cold" feet, and the presence of infected toes with cutaneous gangrene—often accepted as proof without further evidence of occluding arteriosclerosis in diabetics. The arterial pulses at the ankles were strong, however, and the color of the feet normal. A sweating test showed absent sweating about the feet and lateral aspects of the lower legs.

At a room temperature of 26.2°C. the average temperature of the left foot

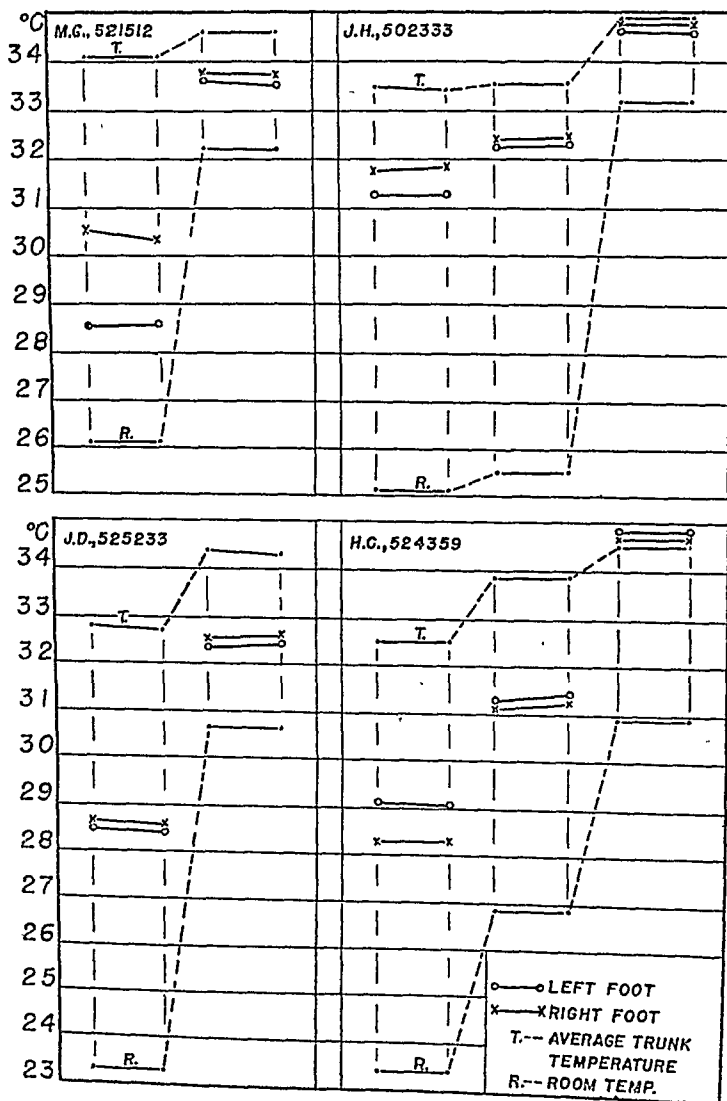


FIG. 1

was $5.4^{\circ}\text{C}.$ less than the average trunk temperature, showing about the normal degree of vasoconstriction. The right foot, however, was found to have in addition to the locally increased temperature about the infected toes an average temperature some $2^{\circ}\text{C}.$ above that of the left, probably due to impaired vasomotor function. At a room temperature of $32.3^{\circ}\text{C}.$ the average temperature of both feet was near that of the trunk, indicating unimpaired peripheral blood flow.

J. H., #502333. The post-appendectomy onset of this patient's diabetic neuropathy has also been referred to above (p. 125). He was tested 15 mos. after the onset when muscle tenderness, generalized aching, stiff and painful joints, and diminished or absent tendon reflexes still persisted. The skin over the hands and lower legs was thin, smooth, and shiny. The peripheral arterial pulses were all palpable and bounding. A sweating test showed diminished sweating below the forearms and absent sweating below the knees. Both hands and feet showed rubor when dependent and a normal color with elevation.

When acclimated to a room temperature of $25.2^{\circ}\text{C}.$ he felt cold, could barely abstain from shivering, and had "gooseflesh" over the trunk and arms but not below the mid-thigh region. The average foot temperature was but some $2^{\circ}\text{C}.$ below that of the trunk, showing greatly impaired vasoconstriction. Nicotine from deep inhalation of cigarette smoke gave no further drop in peripheral temperature and the least exertion, moving or talking, produced an immediate rise in temperature of $0.5\text{--}1.0^{\circ}\text{C}.$ At higher room temperatures the feet were as warm as the trunk, indicating normal peripheral blood circulation.

J. D., #525233. This 66 yr. old male had had poorly controlled diabetes with frequent bouts of mild acidosis for 14 yrs. and neuritic symptoms for 4 yrs. In addition to the neurologic abnormalities—sluggish, unequal, miotic pupils, weak, tender muscles, absent ankle and knee reflexes—he had many small retinal hemorrhages and an atonic bladder. He was 1 of the 2 patients chosen for skin temperature study because arterial pulses could not be palpated at the ankles and the temperature of the feet was usually subnormal. The skin below the knees was thin, dry, and shiny but the color was normal.

When acclimated to a room temperature of $23.4^{\circ}\text{C}.$ he was chilly, uncomfortable, and on the verge of shivering. A fair degree of vasoconstriction was present in the feet, however, as shown by the $4^{\circ}\text{C}.$ difference in the foot and trunk temperature. At $30.7^{\circ}\text{C}.$ the foot temperature was $2^{\circ}\text{C}.$ below that of the trunk, probably indicative of not more than a moderate degree of arterial disease.

H. C., #524359. The detailed case history of this 17 yr. old boy had already been presented (p. 116). There was no clinical reason to suspect peripheral vascular disease. At a room temperature of $23.4^{\circ}\text{C}.$ which made him uncomfortably chilly, somewhat less than the degree of vasoconstriction normally expected was present. Every slight exertion resulted in a rise in the peripheral skin temperature. When exposed to a room temperature of $30.8^{\circ}\text{C}.$ the peripheral temperature exceeded that of the trunk, positive evidence of the adequacy of the peripheral circulation.

Summarizing the results of the skin temperature studies done in the 8 patients

with diabetic neuropathy, these studies failed to disclose occlusive arterial disease which could not be recognized readily by other clinical methods. Even in the less common patient with recurrent infection, cutaneous gangrene, or cold feet without palpable arterial pulsations, evidence of severe circulatory impairment was not obtained. Peripheral arterial and peripheral nerve disease may coexist, of course, in individual patients. There is little evidence, however, in our group of patients with diabetic neuropathy to support the contention that vascular factors are important in the etiology of this type of peripheral nerve disease. The skin temperature studies showed that in patients with other evidence of disturbed peripheral sympathetic nerve function already mentioned—lack of sweating, edema, loss of pilomotor activity, etc.—vasomotor function may be diminished or lost. Excessive vasomotor activity such as occurs in Raynaud's disease, for example, was not encountered.

Vitamin B Deficiency and Diabetic Neuropathy. The etiologic rôle of vitamin B deficiency in the development of diabetic neuropathy has been discussed frequently in recent years. In 1922 Harris (29) compared the neuropathy of diabetes with that of alcoholism and beriberi, as indeed had Charcot in 1890 (10), and suggested the possibility of some common nutritional etiology. Wohl (118) reported in 1926 the case of a diabetic woman who died in a cachectic state of chronically unregulated diabetes who showed definite clinical evidence of avitaminosis. He investigated the nutritional status of other diabetics with neuritic symptoms and concluded that vitamin deficiency was the cause of the nerve disorder. Many authors have since concurred in this opinion (Minot, 119, Wechsler, 120, 121, Cobb and Coggleshall, 122, Vorhaus, Williams and Waterman, 123, Sciclounoff and Broccard, 124, Williams and Spies, 125, Jolliffe, 13, Aring, Evans, and Spies, 126, Sebrell, 127, Youmans, 128, Duncan, 129, and others).

The possibility was then suggested (Jolliffe, 13, Williams and Spies, 125) that diabetic diets in general were deficient in vitamin B content. Although the "cachectic" diabetics with neuropathy so frequently referred to are clinically obsolete, the older types of diabetic diets which they followed were doubtless grossly deficient in many nutritional essentials. One of our recent patients with diabetic neuropathy had continued to follow without medical advice a diet prescribed over 15 yrs. previously. Calculations showed that his diet was not only nearly devoid of calcium but contained less than one-fifteenth the amount of ascorbic acid and less than one-half the amount of riboflavin generally considered essential. The nutritional adequacy including the protein, mineral, caloric, and vitamin content of the modern diabetic diet, however, is an entirely different matter. Joslin (35) has shown that the diabetic now in addition to other nutritional essentials is likely to obtain more vitamins, especially of the B group, than other members of his family. The vitamin content of the diets prescribed in their clinic approximates closely that recommended by the National Research Council (130, 131). Owens, Rockwern, and Brown (132) studied the diabetic diets in a different clinic and found that most diabetic diets were adequate in both vitamin B and C content. The blood ascorbic acid level (133)

in 100 old and in 25 new diabetic patients attending a clinic for those of low economic status averaged higher than in 50 unselected controls. A sampling of diabetic diets served to our hospitalized patients and prescribed in our clinic during the recent past were calculated to show daily vitamin intakes closely approaching or exceeding that recommended by the National Research Council.

Most of our diabetic patients who developed neuritic complications, however, did so while following unrestricted diets or diets qualitatively modified to avoid high carbohydrate foods. This modification in general tends to increase the vitamin B content of the diet. Diet histories in these patients have shown diets of at least average adequacy, certainly adequate enough to maintain other non-diabetic members of the family in excellent health and among whom none ever complained of neuritic symptoms. Jordan (11) investigated the diet in 63 patients with diabetic neuropathy and found only 1 whose diet appeared to have been deficient. Needles (134) made a very careful study of the antecedent diets of 2 diabetic patients who developed peripheral nerve disease and found that the thiamin content had been more than ample.

Other explanations have been advanced to account for the postulated vitamin deficiency leading to neuropathy in diabetics such as defective absorption, loss of water soluble vitamins through polyuria as in the experiments of Cowgill (135), or some increased metabolic need leading to a "conditioned malnutrition" (136). None of these suggestions have been confirmed in clinical or animal investigations. Robinson, Melnick and Field (137) studied the urinary excretion of thiamin in 24 hr. urine specimens and following a test dose of thiamin in a large number of patients including 6 diabetics 4 of whom had peripheral nerve disease. All 6 of the diabetics had normal excretory values. Pollack, Ellenberg, and Dolger (138) likewise investigated the vitamin B₁ excretion in 139 diabetics and found values possibly indicating thiamin deficiency in only 13, a lower percentage than among a control group of unselected individuals. More recently Needles (139) reported thiamin excretion studies in 6 diabetics with well substantiated neuropathy. In 5 of them he found entirely normal values and in 1 a value slightly below normal. Experimentally, Styron and collaborators (140) found that diabetic and non-diabetic rats placed on thiamin deficient diets develop evidence of thiamin avitaminosis with equal rapidity. Whereas, finally, it was once thought that the abnormal carbohydrate metabolism of untreated diabetes could at least be partially corrected by vitamin B administration, this opinion has now been generally abandoned (Trasoff and Bordin, 141, Jackson and Barth, 142, and Owens, Rockvern, and Brown, 132).

Typical lingual and cutaneous signs of vitamin B deficiency (Jolliffe, 137, Jeghers, 143, 144) have been described, however, in diabetic patients on many occasions. Sydenstriker, Geeslin, and Weaver (145) reported observing nicotinic acid and riboflavin deficiencies in 3 diabetics with various complications. The avitaminosis was apparently precipitated by increasing the carbohydrate content of the diet and the insulin dosage. The lesions healed promptly with specific vitamin therapy. A number of diabetic patients with pellagrous skin manifestations were reported by Rudy and Hoffman (146). In several instances

the cutaneous lesions disappeared with nicotinic acid therapy in spite of the diabetes remaining uncontrolled. In 1 patient neuritic symptoms appeared 3-4 weeks after the beginning of nicotinic acid administration, 200 mg. per day. Freston and Laughlin (147) investigated vitamin deficiencies in a group of 93 diabetic children in a summer camp. Twenty-five of the children (26.8 per cent) showed clinical signs of vitamin deficiency, with one exception all of the B group. In 18 cases it was thought that thiamin deficiency was present, and in 10 cases deficiency of vitamin B₂. Twelve of the 25, however, had absent tendon reflexes as the only sign of avitaminosis and this was assumed to represent thiamin deficiency. Poor control of the diabetes, hepatomegaly, and neuritic manifestations were found to parallel each other in incidence.

It is now generally accepted that deficiencies in the vitamin B group tend to be multiple in their incidence. Thiamin deficiency for example is rarely present without some evidence of riboflavin or niacin deficiency. If diabetic peripheral nerve disease were due to B-avitaminosis clinical evidence of such deficiency other than the neuritic disorder should be present in a significant percentage of cases. Such evidence in the cases reported to date, even in the series where this aspect of the problem was emphasized (Rudy and Muellner, 56, Fein, Ralli and Jolliffe, 149, and Needles, 139), has been nearly if not completely absent. In our own patients with diabetic neuropathy lingual or cutaneous signs suggestive of vitamin B deficiency were rarely apparent, even though a large number of them were examined by a group of investigators especially interested in the minor evidences of deficiency apt to be overlooked in the northern states (Field, et al, 148). One patient with a psychopathic personality had been living alone on a starvation diet and on admission there was hyperkeratosis, roughening of the skin over the pressure areas, and a smooth, red tongue. Eight or 10 patients in the series had somewhat reddened tongues without papillary atrophy which became normal when hydration was established. Other than this there was no definite evidence of vitamin deficiency in our group with diabetic neuropathy.

Divergent views are held regarding the efficacy of vitamin supplements in the treatment of diabetic neuropathy. Several factors contribute to this difference of opinion, among them being different criteria employed in diagnosis, lack of familiarity on the part of some investigators with the results of diabetic therapy alone, and the difficulty encountered in disentangling the effects of abnormalities of metabolism possibly due to vitamin deficiency from those due to diabetes mellitus itself. Definite therapeutic benefit, for example, was reported by Fein, Ralli, and Jolliffe (149) who selected 9 patients with peripheral nerve disease from a group of 422 ambulatory diabetics and gave them 10-15 mg. of thiamin daily by mouth for 3-4 weeks. The neuritic disease was mild, however, in every instance. Diabetic treatment was started concomitantly in 2 patients and 3 others had hyperthyroidism which tends to produce an unstable diabetic regulation. Insulin was adjusted as needed for each individual during the period of treatment. A number of atypical cases not responding to treatment were excluded. Owens, Rockwern, and Brown (132) and Rudy and Muellner (56) reported similar if less pronounced therapeutic results after several

weeks or months of vitamin B₁ administration (see below). Needles (139) on the other hand treated 7 patients with more severe and characteristic diabetic neuropathy over an average period of 5½ months with daily doses of 10–15 mg. or more of thiamin. He concluded that thiamin was of no value therapeutically and in fact 2 patients became progressively worse during the time of its administration. Joslin (35), Wilder (150), Levy (151), and White (152) have also found thiamin and other vitamin B fractions ineffective in the therapy of diabetic neuropathy.

Until recently our diabetic patients with neuritic complications were given almost routinely, at least during their hospital stay and in addition to their standard diabetic care, heavy vitamin B supplements in the form of brewer's yeast, thiamin hydrochloride, and niacin. Only after observing the persistence of acute neuritic disturbance for weeks or longer in spite of this treatment were we led to question the value of the vitamin therapy. In judging the clinical response to vitamin B administration the criteria outlined by Aring, Evans, and Spies (126) should be recalled. In true deficiency states a definite response occurs within 7–14 days after adequate vitamin therapy is started. If there is no response further vitamin administration will be unavailing and the therapeutic test is negative.

At least 6 of our patients were given large doses of thiamin orally and parenterally for several weeks or even months by their home physicians while the diabetes remained uncontrolled. In all cases the neuritic disability became progressively worse. In spite of the observations cited above that signs of avitaminosis in diabetics can be cured by specific vitamin therapy even though the diabetes remains uncontrolled (145, 146), I have never seen clinical improvement in diabetic neuropathy by any treatment regimen in the absence of effective diabetic control. Thirty-two of our hospitalized patients were given 10–20 mg. of thiamin orally for 2–3 weeks or longer. About half of them were given 40–50 gm. of brewer's yeast daily in addition. No definite benefit could be ascribed to the vitamin administration. The addition of 200–400 mg. of nicotinic acid daily likewise failed to be beneficial. Daily intramuscular injections of 20–50 mg. of thiamin hydrochloride up to such doses as 1000 mg. in 14 days and 1900 mg. in 25 days (in addition to 40–50 gm. of brewer's yeast daily by mouth) failed to modify the neurologic status in several instances. I have repeatedly observed exquisite muscle tenderness and cutaneous hyperesthesia persist without change through 2–3 weeks of such massive vitamin therapy. In patients becoming rapidly worse as their treatment is started, the addition of vitamin supplements will not prevent clinical progression. A number of recent patients who have been given no vitamin supplements appear to be recovering from their neuropathy as rapidly as any have in the past.

A poorly understood and disturbing phenomenon encountered in the treatment of diabetic patients with associated neuropathy is the acute intensification of the neuritic disease which sometimes occurs shortly after control of the diabetes is undertaken. Neuritic disease may also appear for the first time in those with a history of prolonged diabetic neglect a few weeks after treatment is

begun. Since this occurrence has a bearing on the relation of vitamin B deficiency to diabetic neuropathy it will be discussed in this connection. An illustrative case is presented.

B. S., #521861. This 40 yr. old married schoolteacher was first seen at the University Hospital on 3/15/43. Two years previously increased thirst and polyuria developed and in 8-10 months time despite an "enormous" appetite her weight fell from her average 128 lbs. to 103 lbs. She continued to be weak, underweight and chronically tired. Six to eight months before her hospital visit she consulted several physicians because of the development of severe constipation. Finally glycosuria was discovered and a number of successively lower carbohydrate diets were prescribed which failed to clear the urine of sugar. Her weight continued to fall and finally reached 93 pounds. She was never given insulin. She noted recurrent pains about the left axilla and lower abdomen and occasional numbness and tingling about the feet.

Physical examination on her first visit showed undernutrition and a few areas of psoriasis. The ankle reflexes were diminished and the calf muscles were tender. There was a heavy glycosuria and a moderate ketonuria. The fasting blood sugar was 250 mg. per hundred cc. and the plasma ascorbic acid 0.60 mg. per hundred cc. She was treated as an outpatient for 3 weeks. On a 2800 cal. diet containing 100 gm. protein and 150 gm. carbohydrate, her daily insulin requirement was 25 units of protamine zinc and 15 units of regular insulin before breakfast and 20 units of regular insulin before supper. She became aglycosuric and the fasting blood sugar averaged 100 mg. per hundred cc. She was discharged home clinically improved having gained 15 lbs. in weight and without complaints.

At home the diabetes remained equally well controlled. One week after discharge, however, the muscles of her back and extremities began to ache and feel sore, the skin over her feet to burn, prickle and feel numb. Severe constipation appeared and required the continual use of enemas. Shooting pains "like jabs with a needle" occurred in the extremities. During a period of 2-3 weeks the pain and discomfort increased greatly, especially at night when she "walked the floor and cried," sleep being impossible. Hypodermics of codeine were often needed. Her home physician gave her frequent injections of thiamin hydrochloride and 5 mg. orally every day for the next 5 months.

Seven to eight weeks after the onset of the severe neuritic symptoms slow improvement began. Physical examination at that time showed average nutrition, a pink tongue without papillary atrophy, and no cutaneous signs of vitamin deficiency. There was pronounced generalized muscle tenderness. The right achilles reflex was absent, the left one greatly reduced. The sense of touch was absent and that of pain diminished about the feet and lateral aspects of the lower legs.

During the following weeks slow improvement continued and the use of codeine was terminated. Persistent constipation occasionally alternated with diarrhea. Anorexia especially in the morning lasted for a period of 2-3 weeks and her weight fell 7 pounds.

Six months after the onset of the neuritic symptoms she was able to resume work. Some numbness and painful tingling at the ankles remained and her calf muscles became sore with any more than the minimum of walking. Neurologic examination revealed no definite abnormalities. The complaint of diminished visual acuity led to the discovery, for the first time, of numerous punctate retinal hemorrhages, some of them in the macular regions, and scattered areas of soft exudate, bilaterally.

One year after her visit her only complaint was mild burning and cold feelings about her feet at night. An ophthalmologist found only a few punctate hemorrhages in the peripheral regions of the retina and no exudates.

Twenty of our 125 patients (16 per cent) with diabetic neuropathy became much worse in this way some 2 or more weeks after diabetic treatment was started. It is unlikely that this would have occurred in the natural course of

the neuropathy since the various precipitating factors mentioned above (p. 125) were absent. In 7 cases a definite relapse in diabetic regulation preceded the exacerbation. In several cases alternating hyperglycemia and hypoglycemia with insulin reactions occurred during the course of regulation, while in others the adjustment was perfectly uneventful. Many patients, and occasionally physicians, tended to blame the use of insulin, either the regular or the protamine zinc variety, for the neuritic exacerbation. Caravati (153) described this phenomenon as "insulin neuritis". There were 4 patients in our series who became worse when placed on low carbohydrate diets without any insulin being used. The use of either regular or protamine zinc insulin may be followed by intensification of the neuritic disorder, but persistence in the use of either one or both will lead to a good clinical result if good diabetic regulation is attained thereby for an adequate length of time. I have seen no reason whatsoever to incriminate the use of insulin in the etiology of diabetic neuropathy.

Since the suggestion has been made that increasing the carbohydrate utilization and insulin dosage during diabetic regulation may precipitate vitamin B deficiencies (145), we have sought for evidence in this regard. Cutaneous and lingual abnormalities suggestive of this type of deficiency were never observed during treatment even when the neurologic condition became acutely worse. Vitamin B therapy in these cases as in the others have been a failure. The vitamin content of the diets followed by the patients who had neuritic exacerbations is of interest. Accurate information was available in the case of four of these patients, including the patient cited in detail, in whom there was no question as to the absence of dietary infraction. The amount of thiamin, riboflavin, niacin, and ascorbic acid in their daily diets as calculated from standard food assays (154, 155, 156) is tabulated (Table IV). The amounts compare favorably with those recommended by the National Research Council. Whatever the cause of the exacerbation of the neurologic disorder which sometimes follows the beginning of diabetic treatment may be, we have no evidence of an induced vitamin B deficiency occurring at this time.

Diagnosis. The diagnosis of diabetic neuropathy, although not difficult, is generally one of the least precise clinical diagnoses. It has been said that random aches and pains are often designated as "neuritis", but just as often characteristic symptoms are ignored and conspicuous signs overlooked due to inexpert neurologic examination. It is well known to all physicians who treat diabetic patients that muscular weakness, aches and pains, are almost constantly present in conditions of acute diabetic non-regulation. Muscle tenderness, cutaneous hyperesthesia, and diffuse abdominal pain even with abdominal rigidity are commonly seen in diabetic acidosis and dehydration (15). With treatment of the acidosis and hydration these symptoms and signs subside completely. While some authors refer to this as "hyperglycemic neuritis" (Jordan, 11) there is scant justification for interpreting it as evidence of organic disease of the peripheral nerves. There is little doubt, however, that an acute disturbance of nerve function occurs at this time due to the same causes which, if they remain uncorrected long enough, lead to more permanent nerve damage. The diagnosis of diabetic

neuropathy should not be made unless neuritic symptoms are or have been present and unless there are, in addition, definite signs of neurologic abnormality, which persist well beyond any period of acute diabetic non-regulation.

Although diabetic peripheral nerve disease may occasionally occur early in the course of diabetes, this diagnosis will usually be wrong if the characteristic background of months or years of grossly uncontrolled diabetes is not present. In poorly treated or careless diabetics neuropathy should always be suspected along with other complications such as retinopathy and hepatomegaly. Loss of a considerable amount of weight, or failure to gain weight if the patient is young, will usually have occurred. A history of the neuritic disturbance being intensified or precipitated by factors which aggravate the diabetic status is a helpful point in diagnosis. The associated autonomic nerve disease resulting in gastro-

TABLE IV

Vitamin Content of Diabetic Diets in Patients with Neurologic Exacerbation Following Treatment

	DIET COMPOSITION			THIAMIN	RIBOFLAVIN	NIACIN	ASCORBIC	TIME ON DIET
	Calories	Protein	Carb.	mg./day	mg./day	mg./day	mg./day	
B. S. #521861	2800 NRC allowance	100	200	2.2 1.7	2.94 2.5	13.6+ 17	169 70	4 weeks 1
F. F. #522095	2400 NRC allowance	80	150	1.9 1.5	2.6 2.2	15-18 15	70 70	3 weeks
R. P. #521103	2800 NRC allowance	85	175	1.75 1.7	2.75 2.5	14.5+ 17	140 75	11 weeks
T. F. #519430	3200 NRC allowance	120	250	2.3 2.0	2.68 2.9	15.6+ 20	98 75	3 mos.

intestinal, genito-urinary, orthostatic blood pressure abnormalities, etc., has already been emphasized as a part of the clinical picture of diabetic neuropathy.

Many authors have described a type of diabetic peripheral nerve disease as pseudotabes (3, 10, 11, 15, 28, 27, and 157). Pupillary abnormalities, shooting pains, absent tendon reflexes, and ataxia are some of the clinical characteristics included as a part of this syndrome. Among our group of patients with moderately severe or severe diabetic neuropathy, I have been unable to segregate any well demarcated pseudotabetic group. The proposed differentiating characteristics were so commonly present that the majority could perhaps be called pseudotabetic. The term pseudotabes, aside from considerations of objectionable terminology and its frequent application to other clinical conditions, is of little descriptive value in this condition and might well be dropped. There is

no doubt, however, that syphilis and diabetes can produce a remarkably similar neurologic condition, difficult to distinguish with clinical certainty. We have presented a case (T. F., #519430, p. 119) where diabetic neuropathy developed in a patient who had been treated for syphilis. Although serologic tests were negative during the period of rapid clinical progression many observers believed that lues could not be excluded as an etiologic factor in his illness.

Etiology. Many of the factors that bear on the important problem of the etiology of the peripheral nerve disease associated with diabetes mellitus have been referred to in detail above. We have seen that this complication makes its appearance only after months or even years of grossly uncontrolled diabetes. This lack of control is evidenced by the duration and gravity of the clinical symptoms, the known hyperglycemia and glycosuria, the amount of body weight lost, the presence of other diabetic complications, etc. It has long been known that there is no correlation between the severity of the diabetes or any one acute complication of diabetes such as coma, acidosis, or ketonuria and the incidence of diabetic neuropathy. Fifty-six per cent of our patients, for example, had never had ketonuria demonstrated even at the height of their diabetic non-regulation. There is a striking correlation, however, between diabetic neglect of a degree permitting the patient to survive in a debilitated state of health, without succumbing to the acute complications of diabetes, and the ultimate development of neuritic complications. A review of the relevant information available justifies the opinion that neither occlusive vascular disease nor a primary or conditioned vitamin B deficiency plays a definite etiologic rôle. From our clinical study the conclusion is inescapable that diabetic neuropathy is not only truly "diabetic" in etiology but results from the abnormal metabolism of chronically unregulated diabetes.

Beyond the association of diabetic neuropathy with chronically unregulated diabetes any detailed metabolic explanation of the neuritic disease is as yet speculative. Insulin deficiency, in a manner not as yet understood chemically, leads to interference with carbohydrate utilization. When the diabetic by reason of insulin lack cannot utilize carbohydrate in an amount adequate to satisfy his metabolic needs, protein and fat, the latter especially, are oxidized to meet energy requirements (Stadie, 158). A considerable fraction of the fat undergoes a preliminary oxidation in the liver to ketone bodies, which are then completely oxidized peripherally. Ketones are not abnormal metabolic products, accordingly, and cannot be considered toxic or harmful to nervous or other tissue. When catabolism of fat exceeds a certain maximum, about 150 gm. per day (158), ketonuria appears and this in turn leads to the development of diabetic acidosis (Mirsky, 159). Our clinical evidence indicates that peripheral nerve disease arises when these metabolic adjustments consequent to insulin deprivation fail to maintain adequate nutrition. In considering the metabolic origin of diabetic neuropathy the carbohydrate deprivation may be paramount, but the excessive oxidation of fat possibly leading to peripheral demyelination (160) as well as the protein breakdown which occurs cannot be ignored.

It is well established that under normal conditions carbohydrate is the prin-

cial type of foodstuff utilized in the metabolism of nervous tissue (Quastel, 161). It would not be unreasonable to postulate that any disease interfering with carbohydrate utilization might lead to neuropathy. Thiamin deficiency, perhaps the commonest and best understood cause of peripheral nerve disease, produces a "biochemical lesion" in carbohydrate metabolism wherein there is a failure of pyruvic acid oxidation (Peters, 162) with the accumulation of this substance and lactic acid in the tissues. No comparable metabolic abnormality is known to occur in diabetes (Beuding, Wortis, and Fein, 163, Joslin, 164). Sinclair (165) has recently emphasized the possible rôle of malnutrition in the pathogenesis of peripheral neuropathy. He states that arsenic, a well known cause of peripheral nerve disease, is now known to interfere in a manner similar to thiamin deficiency with carbohydrate metabolism and suggests that other known toxic agents may exert their harmful influence similarly. If abnormal carbohydrate metabolism, leading in effect to neuron starvation, proves to be a common denominator in different types of peripheral neuropathy, it is likely unimportant as regards the end result if the defect occurs at the 6 carbon stage, as in diabetes mellitus, or at the 3 carbon stage, as in thiamin deficiency. The therapeutic considerations, however, are obvious. Our clinical experience as to the effect of treatment of diabetic neuropathy with insulin as compared to the results with thiamin agree with the prediction of Meiklejohn (166) in this regard.

Treatment. The successful treatment of diabetic neuropathy requires first of all expert diabetic management. Problems common to any group of neglected diabetics, to whatever circumstance this may be attributed, will be encountered. Lack of cooperation from the patient may preclude effective treatment although the majority of those who have previously regarded their disease lightly, or have even been definitely uncooperative, are so forcibly impressed with the results of their negligence when neuritic complications appear that they will adhere to any regimen promising relief. There is no indication for unusual types of diets. Standard diabetic diets of average carbohydrate content have given us satisfactory results. All diabetics with neuropathy, with perhaps rare exceptions, should be given insulin at least for the duration of the active neuritic disease. Although well over half of our diabetics who developed neuropathy had only mild diabetes during the early years of their disease, a greatly increased need for insulin accompanied the metabolic "decompensation" which appears to be responsible for the development of the neuropathy. We have seen many patients with this complication who, having taken only small amounts or no insulin previously, will require 80-100 units or more daily before satisfactory diabetic control will be established. Unlike the diabetic whose treatment is begun soon after the disease appears or whose treatment is resumed after a temporary lapse, this need for large amounts of insulin will persist for months if not permanently. Early in the course of treatment a relative insulin sensitivity is common and hypoglycemia is easily produced. Because of the insulin sensitivity and the extreme instability of the diabetic status, protamine zinc insulin supplemented by at least 2 doses of regular insulin given before breakfast and supper daily is advisable. The practical suggestions of Butler (167) have been useful in adjust-

ing the dosage. Insulin reactions should be carefully avoided since the patient's cooperation may be jeopardized and the risk of temporary or lasting neuritic exacerbation increased. The insulin dosage should be gradually increased as necessary over a period often of several weeks. Great care should be exercised to avoid relapse in control, especially as activity is resumed, since loss of control is apt to result in an acute aggravation of the neuritic disease. Diabetic control should not be considered satisfactory until an adequate diet has been provided, no more than traces of glucose appear in any urine specimen, the fasting blood sugar averages 80-100 mg. per hundred cc., and the patient is free of insulin reactions. The diabetic regimen may be simplified later when the neuritic manifestations have subsided. We have seen no benefit from the addition of vitamin supplements unless there are clinical indications apart from the neuritic disease for such medication.

The peripheral nerve disease due to diabetes is in many cases an exceedingly painful affliction, and its persistence over a period of weeks or months is disturbing to the most stoic personality. Symptomatic treatment is a major problem in these cases. Salicylates, support of the bed clothes with a cradle, warm bakes, cool baths, ice packs, etc., are helpful measures at different times but often fail to provide tolerable comfort. Opiates are then required and should not be denied even though addiction is a possible danger. When severe pain refractory to symptomatic treatment is well localized or even restricted to the territory of a single peripheral nerve, local anesthesia, nerve crush, or nerve section might be considered, but our limited experience in this regard has not been encouraging. Sore and tender muscles which ache and cramp at night are made worse by exercise and activity, and are an indication for complete bed rest. During rehabilitation activity productive of muscle tenderness should be prohibited.

The prognosis in diabetic neuropathy, as has often been noted (9, 11, 25, 35, 37, 56, 157, and others) is good, especially in the younger age groups and in those free of complications such as perforating ulcers, neurotropic joint destruction, etc., provided that treatment is begun reasonably early before permanent nerve damage has occurred and that satisfactory diabetic control can be maintained over an adequate length of time. The time required for recovery varies according to the severity of the neuritic disease. In mild cases a few weeks will be required, in moderately severe cases 6-12 months, and in severe cases 1-2 years. Residual neurologic signs will often persist indefinitely.

GENERAL CONSIDERATIONS

Diabetes mellitus is one of the medical diseases in which neurologic complications are not infrequent. For over 50 years it has been known that a type of peripheral nerve disease is prone to result in some obscure way from the abnormal metabolism of diabetes. This tendency is evident from the fact that during periods of diabetic non-regulation, dehydration and acidosis, an acute disturbance of nerve function commonly occurs which promptly subsides with diabetic treatment. The term diabetic neuropathy refers to the more permanent signs

and symptoms of peripheral nerve disorder which persist for weeks or months in spite of the resumption of good diabetic control and which, almost without exception, appear to develop only after months or years of grossly neglected or mismanaged diabetic treatment. All degrees of neuritic disease, from the mildest to the most severe, painful, paralyzing types, may result from diabetes. The facile cure of this complication by the administration of vitamin products, as in the comparable neuropathy due to chronic alcoholism (168, 169), is not a clinical reality. The unusual tendency of diabetic neuropathy to involve the autonomic nerves results in such extraordinarily diverse clinical manifestations of the neuritic disease as neuropathic (Charcot) joints (170), grossly disturbed gastrointestinal and genito-urinary function, abnormal orthostatic blood pressure regulation, etc.

The significance of neuropathy in diabetic patients exceeds merely that of a complication occasionally necessary to recognize and treat. Since one of the major aims in diabetic treatment is the avoidance of complications, both immediate and remote, their early recognition is an important matter for anyone who treats this disease. Acidosis and coma are well recognized and comparatively easily treated acute diabetic hazards. Occlusive arterial disease, diabetic cataracts, and advanced stages of diabetic retinopathy are late complications representing irreversible organic changes, which diabetic treatment will not alleviate and for which other treatment offers but poor compensation. Neuropathy, along with early stages of retinopathy and hepatomegaly, should be emphasized as reversible diabetic complications always a warning to both physician and patient of inadequately controlled diabetes which in the course of time, if uncorrected, will lead to widespread and permanent degenerative changes. At least 50 per cent of all diabetics will survive with little or no treatment for many years. In them the ultimate development of degenerative complications is the only criterion by which the adequacy of their treatment can be judged. The proposed minimum standards of diabetic control (19) may protect most patients from neuritic complications, but the margin of safety appears to be very slight. Outright failure will result from this type of treatment once neuropathy has developed.

The importance of peripheral nerve disease as a predisposing factor in the development of infections about the feet, so incapacitating to diabetic patients, is a subject deserving of further study. McKittrick and Root (52) found in more than a third of their patients with diabetic gangrene that the infection could not be attributed to primarily vascular factors, and that striking degrees of hypesthesia were often present especially in those who had so-called perforating ulcers. Wilder (150), also, expressed the opinion that indolent infections about the feet in diabetics may be dependent on the presence of peripheral neuritis. We have seen many patients with peripheral diabetic neuropathy who develop serious foot infections that with conservative treatment heal and remain well. Four of our patients with severe neuropathy developed necrotic cutaneous lesions about the legs, so-called necrobiosis lipoidica diabetorum (171), and in others vesicles that tended to become infected occurred in areas of sensory impairment.

Anesthetic extremities may well be injured oftener than usual. Peripheral sympathetic nerve degeneration may result in an increased cutaneous vulnerability, and impair the mechanisms by which infections in the tissues once introduced are localized.

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HISTOPATHOLOGY OF THE CENTRAL NERVOUS SYSTEM AFTER EXPOSURE TO HIGH ALTITUDES, HYPOGLYCEMIA AND OTHER CONDITIONS ASSOCIATED WITH CENTRAL ANOXIA¹

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CONTENTS

I. INTRODUCTION.....	161
II. ANOXIA	
1. Effects of breathing mixtures low in oxygen at sea-level barometric pressure..	162
2. Reduced barometric pressures.....	166
III. ASPHYXIA	
1. Asphyxia neonatorum.....	175
2. Delayed death following suicidal hangings.....	177
IV. ISCHEMIA	
1. Arrest of the circulation.....	180
a. Spinal cord.....	181
b. Cerebrum.....	182
2. Acceleration.....	194
V. CARBON MONOXIDE POISONING.....	195
VI. ANESTHESIA	
1. Nitrous oxide.....	198
2. Other anesthetics.....	200
VII. HYPOGLYCEMIA.....	201
VIII. DISCUSSION.....	203
IX. BIBLIOGRAPHY.....	204

I. INTRODUCTION

Interest in the effects of oxygen lack has lately become widespread because of war-time high altitude flying. Armstrong (15) and others have called attention to the occurrence of a progressive gradual decrease in the "ceiling," *i.e.* tolerance for altitude, of aviation personnel, and in the past considerable attention has been focussed upon the possibility that this reduction in altitude tolerance, as well as the phenomenon of "pilot fatigue," might be etiologically related to progressive damage to the cerebral neurons incident to repeated anoxic episodes. However, the experiences of flight surgeons in squadrons operating in combat areas indicate that the causes of "pilot fatigue" are to be sought rather in psychoneurotic disturbances unassociated with oxygen deficiency. With efficient methods of oxygen administration, the alveolar oxygen tension can be maintained at approximately sea-level values up to about 35,000 feet. But in flights above 40,000 feet, air crews become seriously anoxic even though they breathe 100 per cent oxygen. Pending the generalized adoption of pressur-

¹The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or as reflecting the views of the Navy Department or the naval service at large.

ized compartments, anoxia is thus still a factor in stratosphere flying and a consideration of its possible ill effects upon the nervous system is, therefore, of practical importance.

That anoxia alone can cause changes in the nerve cells of the cerebrospinal axis is a belief widely entertained. Review of the experimental and clinical work on changes in the central nervous system induced by high altitude anoxia indicates that the lesions described are similar to those following asphyxia, ischemia (or anemia), carbon monoxide poisoning, anesthesia, inanition, vitamin deficiency and hypoglycemia. Clinically, a similar picture is also seen after death from pneumonia, pertussis, eclampsia, and narcotic poisoning. It is apparent that these conditions all present certain common features. They involve a deficiency, either of material metabolized by the nervous tissue, or of substances without which the metabolic processes cannot be carried out. In some instances a third stage occurs in which waste metabolites cannot be removed. We believe that analysis of the similar histopathology in these various conditions may serve to elucidate a common etiological background and thus establish a firmer basis for therapy, as well as a deeper understanding of the interrelations between the physiology and pathology of the brain and spinal cord.

II. ANOXIA

1. *Effects of breathing mixtures low in oxygen at sea-level barometric pressure*

In 1918, Martin, Loevenhart and Bunting (186) described the morphological changes in the tissues of rabbits exposed to low oxygen tensions. Ten animals breathed mixtures low in oxygen averaging 7.98 per cent for four to ten days. Macroscopically there was no evident abnormality in the brain or spinal cord. No further description of the central nervous system was reported, although hyperplastic changes were seen in the bone marrow and thyroid gland, and degenerative changes leading to necrosis were observed in the heart and glandular organs. These changes were most marked in parts of the organ most distant from its blood supply, *e.g.*, the central zone of the liver lobule and the inner part of the heart wall. Comparable changes were found in 1928 by Rosin (223) in guinea pigs.

Campbell (41, 42) observed that animals subjected to mixtures low in oxygen showed minor lesions of the central nervous system strikingly similar to those observed in rabbits, guinea pigs, rats and mice exposed to carbon monoxide for periods ranging from 15-54 days. These changes consisted of congestion of the brain and some evidence of chromatolysis of the ganglion cells. In a detailed study of hypoxemic changes in the central nervous system reported in 1938, Rotter (224) subjected three guinea pigs, in a closed vessel, to a stream of oxygen-nitrogen mixture until the animals died 174, 189 and 235 hours after the beginning of the experiment. Each day the animals were returned to normal air and fed. During the first 48 hours of the experiment the oxygen tension was gradually lowered to six to seven percent and subsequently never rose above 7.4 per cent (equivalent to an altitude of 8000 meters) until the end of

the experiment. Three additional animals were subjected to these same conditions for 80 and 100 hours after adaptation, and then sacrificed by decapitation. Nissl preparations of the central nervous system of the animals which died spontaneously showed ganglion cell changes in the medulla characteristic of Nissl's "Schwere Ganglienzellerkrankung." There was clumping of chromatin around the nucleoli which were darkly stained, and in some cells the entire nucleus was markedly hyperchromatic. These changes were regarded as irreversible, and the lesions were found to be most widespread in the basal ganglia, as well as in the nuclear groups situated in the floor of the fourth ventricle. The Purkinje cells of the cerebellar cortex were seen to be markedly degenerated, but the cerebral cortex was normal except for small foci of ganglion cell degeneration in areas adjacent to the median longitudinal fissure. Control animals killed 80 to 100 hours after the beginning of exposure showed no ganglion cell change. Rotter stated that the neuro-pathological changes produced in these experiments were more widespread than those reported in animals subjected to decompression by Büchner and Luft (35, 36). In contrast to these findings, Van Bogaert, Dallemagne and Wégria (274) could find no histological abnormality in the brain, cord or peripheral nerves of monkeys subjected to anoxemia by nitrogen replacement of the oxygen in the air. In two animals some demyelination was apparent but was assumed to have been present before the experiment.

In a comparison of the anatomical changes produced by anoxic and insulin shock, Tannenberg (264) subjected 38 rabbits to low oxygen-high nitrogen mixtures for repeated short periods lasting from 15 to 60 minutes. From 1 to 51 of these episodes of anoxic shock were induced in the various animals within 1 to 60 days. Twenty-nine other rabbits were given repeated insulin injections in amounts sufficient to induce convulsions and coma. The neuropathological picture in these two groups of animals was found to be much the same. There was slight to severe degeneration of the nerve cells together with reactive glial proliferation. Tannenberg believes that the severity of the morphological changes is related to the frequency of the anoxic shocks and the severity of the clinical response to the administration of insulin. The pathological changes noted were particularly impressive in the large pyramidal cells and were also seen in the Purkinje cells of the cerebellar cortex as well as in the hippocampus, medulla and spinal cord. The lesions did not appear to be localized in any specific nuclei, but in some areas there was evidence of profound physiological reaction, and almost all the nerve cells in several circumscribed areas of cerebral cortex or hippocampus were destroyed. These foci were attributed to adverse vascular reactions during the seizures. Tannenberg based the pathogenesis of the lesions in insulin shock on deprivation of the carbohydrate which is the nerve cell's foremost nutritional material (Himwich, Bowman, Wortis and Fazekas, 126). In anoxic shock the lesions were ascribed to lack of oxygen which is indispensable for the utilization of the substrate. The same nerve cells are affected in either insulin or anoxic shock, but there are some differences in the morphological appearances of the cells in the two conditions. In insulin shock, the cells are faded and show up as bleached areas in stained preparations, whereas

after anoxia the ganglion cells are shrunken and darkly stained as if calcified. It is noteworthy that changes following abrupt arrest of the circulation (during which the cells are deprived of both oxygen and carbohydrate), include faded "ghost" as well as darkly-stained, shrunken, pyknotic cell-bodies.

Yant, Chornyak, Schrenk, Patty and Sayers (293), in a detailed study of the effects of asphyxia on dogs, found severe hyperemia in the brain as a whole after comparatively rapid asphyxia by exposure to sea-level atmospheres deficient in oxygen. The hyperemic capillaries had the same appearance as in an artificially injected preparation and both the meningeal and cerebral vessels were greatly dilated and tightly packed with red blood cells. Stasis was marked throughout and numerous petechial hemorrhages were seen, especially in the brain stem. There was a remarkable difference in the degree of injury to the nerve cells in various regions of the same brain. A striking feature was the severe damage in the neurons of the outer granular layer of the dog's cortex, especially in areas showing good cell and fiber lamination. There was complete lysis of the Nissl granules in these cells. Their nuclei were distorted and faintly stained. In some instances a pole or fragmented nucleus was all that was left of the original cell body. The neurons in the deeper cortical layers showed definitely less damage. Edema was slight and usually seen perineuronally in the most markedly damaged areas. Some of the neurons in the cortex, especially the small pyramidal cells, were shrunken and diffusely stained. In the thalamus the degenerative changes were more severe than in the corpus striatum, while the large polygonal cells in the reticular formation, the nuclei of the hypoglossal, abducens, trochlear, and oculomotor nerves, and the nucleus ruber as well as the motor neurons of the spinal cord showed relatively little change.

In rats exposed to similar conditions of oxygen deficiency certain differences in the brain reactions were found as compared with those of dogs. The non-olfactory cortex, with the exception of the large polygonal-shaped cells, showed practically no damage. In the large cells, there was marked central chromatolysis, even to the extent of complete lysis and destruction of some of the cell bodies in rats 'asphyxiated' for one hour and twelve minutes. The olfactory cortex, both the bulb and the hippocampus, exhibited pathological changes, especially in the large cells in the stratum lucidum. The large polygonal-shaped cells, such as those in the somatic efferent nuclei and nucleus ruber, and the motor anterior horn cells of the spinal cord, displayed relatively marked damage. In the dog, cells of these same groups showed the least damage. Thus in the rat the cells of the cortex, especially those in the outer granular layer, the thalamus, the sensory and correlation centers throughout the brain stem and the visceral efferent nuclei, were the most sensitive; while the nucleus ruber, the nuclei of the oculomotor, trochlear, abducens, and facial nerve, the large polygonal shaped cells in the reticular formation and the motor neurons of the anterior horn of the spinal cord were the least susceptible in the dog. Motor cells, least susceptible in the dog, appear to be much more sensitive to oxygen deprivation in the rat. Two types of nerve cell changes could be differentiated: some neurons became shrunken and stained diffusely; others showed varying degrees

of chromatolysis. The definite and remarkable differences noted by Yant *et al* in the susceptibility of nerve cells in various regions of the same brain and in the same type of cells in different species are especially noteworthy, and it is of interest that essentially the same findings have been reported after ischemia and complete anemia of the brain (Kabat and Grenell, 146, Grenell, 97, 98).

In 1940, Thorner and Lewy (268) immersed guinea pigs and cats in a stream of pure nitrogen. In one group, animals were rendered anoxic for various periods of time and then decapitated one-half hour after removal from the chamber. After 15 seconds exposure there were no demonstrable microscopic changes apart from a few miliary hemorrhages over the cerebral hemispheres. In the brain of an animal exposed for 30 seconds, the nerve cells showed reduced affinity for the stain and the glia cells were pyknotic. There was no visible decrease in the number of neurons. With 60 seconds exposure, fresh perivascular hemorrhages were observed and some nerve cells were seen to be permanently damaged, especially some large cells in the deeper layers of the cerebral cortex. These cells were swollen and the cytoplasm poorly stained or completely colorless. Sublethal periods of oxygen deprivation were thus seen to produce changes in cortical cells, many of which were irreversibly damaged. In one guinea pig and one cat sacrificed directly after exposure to the nitrogen atmosphere, there were only vague nerve cell changes, and the cortical architecture was essentially normal as were the hippocampus, the Purkinje cells, the ependyma and the blood vessels. Apparently, therefore, a survival period is necessary for the changes caused by pure anoxia to become histologically apparent.

One guinea pig was sacrificed in the nitrogen chamber after nine previous exposures, and another after twelve periods of exposure. In these animals there were numerous subpial hemorrhages in the brain. The nerve cells of the deep cortical layers of the hippocampus and the subiculum were pale, with shrunken and pyknotic nuclei, and foamy cytoplasm. Foci of blanching were present in the cortex, probably in connection with fibrosis of small arteries. Some nerve cells had disappeared completely. In larger cerebral arteries the media was rich in fibroblasts and encrusted with granular material giving the reaction of calcium.

In animals dying 8 to 48 hours after one or repeated immersions the cortex was profoundly damaged. The nuclei of the nerve cells were pyknotic and retracted from the cytoplasm of which only the marginal zone stained with basic dyes. The cortex seemed almost devoid of ganglion cells. The granular layers showed marked neuronal injury and nerve cells in the hippocampus and the Purkinje cells presented a typical picture of advanced ischemic necrosis. In one animal, nerve cells of the basal ganglia and brain stem were also involved. Similar changes were observed in animals decapitated after repeated anoxia. In one guinea pig the cellular degeneration in the cortex was laminar, while in the cat a patchy degeneration was observed. As far as could be shown in this limited number of animals, nerve cell damage appeared to increase with repeated anoxic periods up to a certain point beyond which nerve cell loss did not progress further.

Summary. Save for the early work of Martin, Loevenhart, and Bunting (186) and the negative findings of Van Bogaert, Dallemagne and Wégria (274) on macaques, the open literature thus offers convincing evidence of lesions of the nervous system resulting from oxygen deficiency alone. These pathological changes involve both ectodermal and mesodermal tissues of the central nervous system—ganglion cells, glial cells and blood vessel walls all being vulnerable. Involvement of the ganglion cells includes all stages of cellular damage from minor degrees of chromatolysis and reduced affinity for stains to swelling and shrinkage of the cells with disorganization and diffuse staining of the cytoplasm as well as distortion and fragmentation of the nuclei. In some instances of repeated exposure, ganglion cells may be completely destroyed. Glial changes are reported as mainly degenerative but some proliferation has been observed.

Vascular disturbances in the form of hyperemia, subpial and perivascular hemorrhages are a prominent feature and probably the parenchymal changes observed are attributable not only to the direct effect of anoxemia but also are to be considered as secondary effects of disturbed blood supply.

The neuronal lesions are widely distributed and although the hippocampus and the Purkinje cells of the cerebellum are particular sites of election, abnormal cells are also seen in the basal ganglia and brain stem and, less frequently, in the spinal cord. Lesions of the pyramidal cells have been noted although in Rotter's experiments on guinea pigs, the cerebral cortex was entirely normal. There is no obvious relationship between the localization of the lesions and the severity or duration of anoxia. Sublethal single exposures to pure nitrogen for as brief periods as 30 to 60 seconds result in histologically demonstrable lesions provided sacrifice is delayed a half hour; repeated short exposures produce advanced changes, particularly if death occurs spontaneously some hours after the final period of low oxygen.

2. *Reduced barometric pressures*

Paul Bert's dictum, "*l'autopsie ne montre guère de résultats intéressants*," (25) in reference to deaths due to decompression probably delayed detailed study of the pathological changes resulting from simulated high altitudes. In 1902, however, von Schrötter (241) reported upon histological studies on the central nervous system of guinea pigs and a pigeon decompressed to 200 to 300 mm. Hg. for varying periods. In a guinea pig kept at low pressure for 72 hours, Marchi preparations of the spinal cord showed no definite changes although there were scattered areas of degeneration in the myocardium and fatty infiltration in the kidney tubules and liver lobules, as well as a considerable number of nucleated red cells in the blood. Similar negative results were observed in guinea pigs decompressed for 15, 22 and 74 hours, but in an animal which survived five weeks after a period of reduced pressure lasting two days, fatty infiltration of capillary walls could be seen in the anterior columns at the thoracic level of the spinal cord as well as in scattered areas throughout the brain. In methylene blue preparations it was not possible definitely to rule out pathological changes.

Campbell (41) in 1927 compared the effects of low oxygen tensions at normal

and reduced barometric pressures in rabbits, rats, mice, cats, guinea pigs and a monkey. In general, no definite degenerative changes were detected in brain cells, although some showed less prominence of the Nissl granules. There was little or no deviation from normal to be detected in nerve cells of the medullary respiratory center. Campbell concluded that decompression and breathing mixtures low in oxygen resulted generally in congestion of organs and some fatty degeneration.

In a series of carefully controlled studies in 1935-36, Büchner and Luft (35, 36) decompressed guinea pigs to pressures of 250 to 300 mm. Hg: Control animals were fasted for four days prior to sacrifice so that their nutritional status might be comparable to that of decompressed animals whose appetite was much reduced. The brains and cords were fixed in 96 per cent alcohol and stained by Nissl's method with toluidine blue. In one animal dying after exposure to 250 to 375 mm. Hg. for 123 hours, of which 103 hours were below 300 mm. Hg., there was marked nuclear degeneration, vacuolation of the cytoplasm and loss of Nissl substance in ganglion cells in the floor of the fourth ventricle. Similar but less marked symmetrical changes were observed in the Purkinje cells of the cerebellum as well as in scattered cells throughout the brain stem. No abnormality could be detected in the cells of the cerebral cortex. In animals decompressed for 160, 173 and 178 hours, changes of the same type were demonstrable. In one of these animals there were varicosities along the dendrites of cells in the floor of the fourth ventricle, and some cells in the anterior horn of the spinal cord were observed to be abnormal. The control animals killed by intravenous injection of air after a four day fast showed no pathological changes in the nervous system. The authors noted that convulsions, ataxia and respiratory irregularity near the end of the experiment were associated with the postmortem finding of marked irreversible damage, particularly in the motor cells in the floor of the fourth ventricle and the Purkinje cells of the cerebellum. They believed that changes become more pronounced from cranial to caudal poles of the brain, and called attention to the fact that these findings are in harmony with those of Haldi, Ward and Woo (104) on lactic acid concentrations in the brain after oxygen lack. The latter authors reported an increase in brain lactic acid which was least in the cerebral cortex, moderate in the brain stem and cerebellum and greatest in the medulla.

Büchner and Luft explain the differences in susceptibility of the neurons in various parts of the central nervous system on the hypothesis that medullary centers, being active to the end, suffer greater change, while the cerebral cortex, which becomes inactive early, suffers less from lack. Subsequent investigators have shown, however, that the cells of the cerebral cortex are much more liable to severe damage as a result of decompression than the experiments of Büchner and Luft would indicate.

Luft (176), in 1937, in a comparative study of the effects of hypoxemia on old and young guinea pigs, sought to determine whether the pathological changes previously reported were influenced by duration and intensity of the decompression, and whether their severity could be related to the age and weight of the

experimental animals. Guinea pigs were decompressed simultaneously in groups being left in the chamber until death supervened in 108 to 230 hours. During the first 48 hours the pressure was reduced gradually to 353 mm. Hg. since it was found that in many cases, animals survived a sudden decompression to 300 mm. Hg. or less, for only a few hours. On the third day the pressure was again reduced and subsequently maintained at 250 to 300 mm. Hg. The nervous system was studied in Nissl preparations. In a group of five adult animals dying of exposure to a pressure of 286 mm. Hg., the large ganglion cells in the region of the pons and the cerebral peduncles showed fragmentation of the nucleolus into dark fragments lying against the nuclear membrane. The cytoplasm was scarcely visible or showed only irregular clumping of the Nissl substance. In the floor of the fourth ventricle many large ganglion cells showed alterations in the nucleoli and marked disintegration of the Nissl substance into a fine, dust-like sediment. In some cells the Nissl substance appeared to have been entirely precipitated at one pole of the cell body. In some cases long, drawn out cells with fragmented Nissl substance and swollen dendrites were seen in the *medulla oblongata*. In these cells the nucleus was surrounded by a dark halo and was sometimes to be found at the periphery of the cell. The nucleoli in these nuclei were irregular in form.

A second group of guinea pigs kept at 86 mm. Hg. died 15, 20, 36 and 80 hours after having been removed from the chamber. Characteristic brain lesions consisted of disintegration of the Nissl substance into dustlike granules or a thread-like stroma, and occasional eccentricity of the nuclei. In the medulla, the large motor cells sometimes showed a high degree of thickening of chromophil substance around the nuclei.

In a third group, Luft decompressed young guinea pigs of three weeks average age. All the animals died under decompression, in convulsions. In certain areas of the pons cells were seen with marked changes. The changes in these cells as well as in some cells of the medulla and midbrain were essentially those of fragmentation of the tigroid substance, pyknosis of the nuclei and satellitosis. In some cells the nuclei were absent, while in certain medium-sized cells of the caudal portion of the basal ganglia, the nuclei appeared swollen and indefinite in outline. The nucleoli were fragmented, and the cytoplasm contained a few poorly stained, dust-like granules.

In nearly all animals the most severe brain changes were found in the floor of the fourth ventricle. In general, the damaged cells presented a picture of Nissl's ischemic atrophy and the "homogenizing" changes of Spielmeyer. It is of interest that Wustmann and Hallervorden (292) found similar cell changes in patients dying several hours after Trendelenburg's operation for acute pulmonary embolism. In these cases, however, the pathological disturbances were most pronounced in the cerebral cortex, cerebellum and basal ganglia.

In young animals the changes in the central nervous system observed by Luft were more advanced than in older animals, although in the younger group there was no evidence of the myocardial lesions commonly found in the adults and believed by Luft to be the main cause of death in the older animals. There

was no relation between the intensity and duration of the decompression and the severity of the lesions. Luft's observation of more profound injury to the neurons in young guinea pigs is difficult to reconcile with the findings of Kabat and Dennis (145), Kabat (142) and others of a greater resistance of young animals to arrest of the cephalic circulation.

In further decompression experiments on guinea pigs in 1937-38, Luft (177) called attention to severe degenerative phenomena in the Purkinje cells and cells of the basal ganglia. In these areas, degenerated cells were seen to lie closely adjacent to neurons of completely normal appearance. A similar picture has been observed in dogs after arrest of the circulation of the brain by Kabat and Grenell (146), who urge this in favor of the possibility of the occurrence of localized metabolic changes within the brain.

In 1939, Dellaporta (60) described experiments in which he subjected young male guinea pigs (weight 300 to 400 grams) to continuous decompression for moderately long periods and subsequently investigated the changes in the central nervous system stained by Nissl's method with toluidine blue. In his first series, he took the animals gradually to 250 mm. Hg. and kept them at that pressure for 11 to 61 hours. These animals showed marked loss of weight during the decompression and in many of them the weight loss continued after recompression, and death occurred spontaneously $37\frac{1}{2}$ to 81 hours after the end of the chamber runs. Weight loss at death was, on the average, 36 per cent of the initial body weight. In the liver there was central necrosis of the lobules and the central nervous system showed marked degenerative changes in the ganglion cells (comparable with Nissl's "schwere Ganglionzellerkrankung"). These changes occurred chiefly in the medulla, the Purkinje cells of the cerebellum, the basal ganglia, the diencephalon and in the region of the central sulcus of the cortex as well as in the hippocampus and the fascia dentata. Only those animals showed pathological nervous changes which continued to lose weight after recompression. Within the limits of the time of exposure used in these experiments, there was no relation between the severity of the nerve cell changes or the mortality of the animals and the duration of decompression.

In a second group, Dellaporta subjected animals to decompression at 250 mm. Hg. for periods ranging from 33 to 104 hours, sacrificing them immediately after recompression. No changes in the central nervous system were found in any of these subjects. *It thus appears that animals surviving an initial decompression—even a long one—do not show histologically demonstrable lesions in the central nervous system if killed at once, although irreversible functional changes have occurred in the cells to such an extent that most of these animals would have been doomed to die within 30 to 80 hours with accentuated neuronal lesions.* This observation is in keeping with the results of most workers who find histopathological lesions in the brain and cord only in animals that die spontaneously or are sacrificed after a definite interval following subjection to hypoxia or anemia. To be sure, as Dellaporta and others have pointed out, animals that succumb during decompression show irreversible changes in the ganglion cells.

Under conditions of decompression such as those prevailing in Dellaporta's

experiments, animals lose weight. This weight loss is attributable to several causes, such as increased fluid loss from body surfaces and the marked anorexia which is characteristic of these animals. It becomes very interesting to know to what extent this starvation factor may operate along with anoxia in the genesis of cerebral damage. Evidence in the literature of the effect of starvation alone on the nervous system is somewhat conflicting; however, Dellaporta found that animals starved to death at normal barometric pressures all showed profound degenerative nervous changes. The animals survived for periods from 147 to 194 hours, sustaining an average weight loss of 44 per cent. In two of these starved animals, five cc. of saline were given intraperitoneally each day but this had no effect either upon survival time or the appearance of the nervous lesions. The brain changes were qualitatively and topographically similar to those observed in the hypoxic group. Quantitatively, there was less marked degeneration in the hippocampus and the fascia dentata.

That nutritional deficiency diseases may produce pathological changes of the peripheral and central nervous systems is well known. Various clinical and experimental cases of inanition and more especially of vitamin deficiency have shown marked histologic changes in the nervous system. For example, lesions ascribed to inanition have been reported by Tarassewitsch (265), Agostini and Rossi (4), Meyers (196), Hassin (110), Urechia and Mihalescu (273), Jackson (136), Garofeanu and Ornstein (82), Andrew (11, 12), Ferraro and Roizin (76) and others.

In human material, Hassin described excess of lipoid granules in the nerve cells, glia cells, the adventitial spaces of the blood vessels, the pia-arachnoid and the choroid plexus while the experimental data presented in Jackson's monograph point to the existence of diffuse degenerative nerve cell changes which vary in intensity from animal to animal. Generally, acute swelling and chromatolysis have been reported. Shrinkage of nerve cells has also been described, as well as varicose atrophy of the dendrites and hypertrophy and condensation of the neurofibrils. Urechia and Mihalescu reported pathologic degenerative changes in the nerve cells of the tuber cinereum in starved dogs, extending to the paraventricular, supra-optic, mammillo-infundibular, pallido-infundibular and interfornicate nuclei. Changes in microglia and oligodendroglia have also been noted.

Ferraro and Roizin (76) found a diversified reaction of the blood vessels, consisting predominantly of hypertrophy, hyperplasia and proliferation. They described localized lesions in many areas of the cerebral gray matter and found that certain regions were more severely damaged by the same amount of inanition than others. In their experiments, neuropathologic changes in the brain affected mainly the nerve cells, which appeared diffusely degenerated. The type of degenerative change most frequently encountered was one of diffuse chromatolysis with more or less pronounced pyknosis of the nucleus. However, nerve cells undergoing shrinkage, ischemic change, or severe type of degeneration of Nissl were also quite frequent. Zimmerman is of the opinion that the lesions described by Ferraro and Roizin are predominantly due to a deficiency of vitamin B₁.

It is quite possible, therefore, that in subjects exposed to prolonged or repeated periods of decompression, nutritional defects resulting from anorexia and other causes associated with flight, may be significant factors in determining the degree of damage sustained by the nervous system under conditions of low oxygen. One is prompted to ask whether decompression alone, apart from malnutrition, will lead to irreversible changes in the neurons, or, putting the question another way, whether by artificially maintaining something like normal nutritional intake, it would be possible to avert the havoc played in the brain by decompression. In an attempt to solve this problem Dellaporta gave guinea pigs forced feeds of buttermilk and glucose during the periods of decompression. These animals sustained weight losses averaging about 17 per cent and in the animals which were examined after death, there were no changes in the brain or cord. Dellaporta admitted, however, that the difficulties of feeding, the fact that the individual feeds were too large and other factors diminished the animals' resistance to the experimental conditions and they therefore did not survive as long as the first group. Consequently, the negative findings are of limited significance.

Dellaporta has suggested that the loss of appetite in decompression might arise as a result of liver damage or might possibly be due to the central nervous disturbance. The hepatic necrosis he assumed to be a primary anoxic phenomenon. It seems that evidence such as that given by Dellaporta is, in part, the basis for the importance which the Germans attach to large and varied diet for aircrews, especially those who carry out long and repeated operational activities at very high altitudes. It is recognized, of course, that adequate diet is essential in maintaining several specific aspects of flying efficiency; that it may play a deciding rôle in mitigating damaging effects on the nervous system appears to be a new thought. One would like to see further comparisons of the histological picture in the central nervous system of animals decompressed with and without special attention to maintenance of body weight and nutrition. As noted below some notice has been given to this problem in the Japanese literature, but apparently no adequate reports exist.

The literature and described lesions in vitamin B group deficiencies have been reviewed by Wolbach and Bessey (289), Hsü Ying-K'uei (133), and Zimmerman (296). The majority of observers have reported degeneration of peripheral nerves, myelin degeneration in the cord, bilaterally symmetrical minute hemorrhagic lesions in the pons, medulla and cerebellum, and hemorrhages into the nuclei around the ventricles. The sequences described are vascular hyperemia, perivascular edema, and, finally, hemorrhage. Hsü noted *disruption* of the cytoarchitectonics of the cerebral cortex, with chromatolysis, shrinkage, ischemia and severe disintegration of ganglion cells of the brain. Zimmerman (296) observed vascular changes, demyelination, hemorrhage, etc., and pointed out the differences between chronic and acute deficiencies, as well as between deficiencies of various portions of the B complex. He believes that peripheral nerve injury constitutes a major feature of the pathological picture in vitamin B deficiency.

From a practical point of view, the weight of flying personnel ought to be carefully watched. If the conclusions drawn from the animal experiments (of Dellaporta and others) can be directed to human problems, one must be alert to the possibility that a loss of weight in an aviator may be coexistent with lowered resistance of the nervous system to high altitude and that continuous flying under such circumstances may produce cumulative pathological lesions in the brain, which may eventually exceed its factor of safety and give rise to serious disability.

Obviously, the problem of the etiology of nervous lesions resulting from decompression is a complicated one. It is clear, however, that in addition to primary oxygen lack there are secondary factors. Various nutritional disturbances may be involved, as Dellaporta's work and other investigations seem to show. That toxic products accumulating as a result of disturbed metabolism may also be important is suggested by the severity of the brain lesions found after complete vascular stasis produced by circulatory arrest.

Following Dellaporta's work, Merk (192) in a comprehensive experimental study of the pathological effects of decompression on the central nervous system, attempted to answer the question whether hypoxia without weight loss would be followed by ganglion cell lesions. He subjected guinea pigs to daily periods of low pressure, and examined the brain stained by Nissl's method. In a first series guinea pigs were subjected for one to two hours daily to atmospheric pressure of 198 mm. Hg., until death occurred spontaneously after several days. In one of these animals which succumbed on the fifth day by gradual respiratory failure, there was homogenization of the cytoplasm with hyperchromatic Nissl substance in the medulla. The nuclei and nucleoli were generally normal, but the cellular processes were deeply stained. In some medullary cells there was destruction and fragmentation of the Nissl substance with shrinking of the nucleus. Marked pyknosis of the nucleus was seen in cells of the habenular nucleus, and changes were also observed in the Purkinje cells of the cerebellum. In the diencephalon, cellular changes similar to those in the medulla and cerebellum were seen. No abnormalities of nerve cells could be demonstrated in the hippocampus or the cerebral cortex. Other animals in the series showed similar changes, although in some instances the Purkinje cells were not involved, nor were changes seen in the cells of the diencephalon. All the animals in this series of experiments show ganglion cell changes. However, they are less widespread than those reported previously by Büchner and Luft. These animals not only maintained their initial weight, but even became heavier during the course of the experiment. Merk concluded, therefore, that decompression alone apart from weight loss, can cause ganglion cell changes.

In a second series of experiments, two animals were given repeated periods of decompression on successive days, lasting from 60 to 190 minutes in the first case, and 10 to 150 minutes in the second. On the ninth day, the first animal was killed by further lowering of the barometric pressure to an equivalent altitude of 12,000 meters. No histopathological lesions could be demonstrated. The second animal, similarly killed on the sixteenth day showed some changes in the medulla and habenular nucleus, but was otherwise normal.

Three guinea pigs subjected to single runs in the decompression chamber at an equivalent altitude of 12,000 meters until death, supported this environment for 110, 70 and 40 minutes respectively. In no case was any change found in the nerve cells. This suggested that single exposures to the point of death do not result in histologically demonstrable lesions and would also indicate that the pathological changes resulting in the brain from repeated decompressions are not due to the last and fatal run alone, but to the summed effects of all the runs.

Since these relatively short single decompressions did not produce lesions, Merk repeated the experiment with longer periods of exposure. An animal subjected to an equivalent altitude of 10,000 meters for eight hours, followed by two hours at 12,000 meters, showed changes in the Nissl substance as well as swelling of the nuclei in the medulla around the hypoglossal nuclei, with pyknotic nuclei and dust-like Nissl substance in the Purkinje cells and in cells of the basal ganglia as well as marked nuclear changes in the habenular nuclei. A single exposure at 12,000 meters equivalent altitude was insufficient to produce the cerebral lesions although the animal's respiration was shallow and irregular during the entire period.

In animals which survived repeated exposures to ceiling pressures over several days, no nerve cell abnormalities were demonstrable. Merk concluded that in single exposures to low pressure there are no irreversible cell changes, provided that the animal survives. In nearly all animals dying rapidly, no ganglion cell changes were visible, whereas marked cerebral changes could be seen in animals which succumbed slowly. A definite period of time must elapse before the cell changes become histologically apparent.

Ambo and Nakamura (8, 9) decompressed rabbits, investigated the associated effects of various food factors, and studied the resultant cerebral damage. Animals decompressed continuously to 260 to 310 mm. Hg. until death five or six days later showed hemorrhages in the central nervous system with enlargement of the Virchow-Robin spaces and swelling of the nerve cells, with eccentric or pyknotic nuclei and chromatolysis. These changes were most intense in the tectal nuclei with slight changes in the basal ganglia, hippocampus and cortex. Some of the Purkinje cells of the cerebellum completely disappeared. It is noteworthy that enlarged Virchow-Robin spaces as well as disappearance of Purkinje cells are frequently found following cerebral anemia.

Animals similarly decompressed after subcutaneous or intraperitoneal injection of 40 or 60 cc. of physiological saline solution, suffered a less marked loss in body weight and survived longer. Changes in the central nervous system were qualitatively comparable to those previously observed, but were much less severe. No instances of cell death were observed. In animals provided with added oxygen during decompression there were no ischemic changes in the ganglion cells, no hemorrhage, and only slight changes in the ganglion cells in the floor of the fourth ventricle. Administration of colchicine or glutathione prior to decompression had little or no effect on resulting neuronal lesions.

In the spinal cord, hemorrhage and demyelination have been observed by

Yohda (294) in rabbits decompressed to 260 to 310 mm. Hg. for four to six days. These changes which have not been commonly noted in the literature after anoxia, have, as previously stated, been observed in cases of inanition and vitamin deficiency.

Altmann and Schubothé (7) studied physiological and pathological effects of anoxia on the nervous system of cats subjected to decompression, in some instances to the point of cessation of respiration. They described all types of nerve cell degeneration of Nissl (with and without accompanying lesions of glia) which they felt it was possible to correlate with the rate at which the lesions were apparently produced. The white matter was almost never affected, but the gray matter showed elective localization of lesions whose gradient of intensity was markedly similar to that described by Yant *et al* (293) as well as by others after occlusion of the cephalic circulation. (In order of decreasing intensity the areas injured were: cerebellum, cerebral cortex, caudate nucleus—not globus pallidus—, lateral geniculate body, nuclei of sensory cerebral nerves, and posterior columns of the spinal cord). In all injured areas only certain types of cells and these in only certain layers showed most marked damage. The authors concluded that there is present a special sensitivity to anoxia which may be locally intensified by vascular disturbances. It is of great interest that they also find similar cerebral pathology after other conditions such as obstruction of the respiratory passages, carbon monoxide poisoning, narcotic poisoning, ligation of the carotid and vertebral arteries, cyanide poisoning and hanging.

Summary. In a brief summary of the effects of decompression upon the central nervous system, it may be concluded that the ganglion cell changes correspond closely to those encountered in animals exposed to low oxygen mixtures at sea-level barometric pressure. The Nissl substance is characteristically fragmented or broken up into fine dust-like particles; the cytoplasm may be vacuolated or homogeneously stained; there may be swelling or shrinkage of cells. The nuclei may be displaced, irregular in shape, shrunken or darkly staining and amorphous. Varicosities of the dendrites are sometimes characteristic. According to the literature, which is mainly from German sources, the cerebral cortex is usually spared although cortical lesions have been described by Dellaporta and by Ambo and Nakamura (8, 9). The medulla and cerebellar cortex are particular sites of election but damaged nerve cells are found scattered throughout the brain stem. In general, there are no changes in the spinal cord.

Animals subjected to single lethal exposures to a simulated altitude of 12,000 meters for 40 to 110 minutes do not show neuropathological changes, nor are lesions present in the brains of animals sacrificed after repeated short, daily, sub-lethal decompressions to this altitude. Exposure to single periods of decompression to 250 mm. Hg. for 33 to 104 hours does not result in histologically demonstrable lesions if animals are sacrificed immediately after the experiment, although such animals usually die spontaneously some days later with marked changes in the brain. In general, pathological changes are most pronounced and widespread in animals succumbing to repeated decompression or dying some days after single exposures to low pressure.

III. ASPHYXIA

1. *Asphyxia neonatorum*

Ford (78) reviewed the literature relative to asphyxia of the newborn, and concluded that trauma is more important than anoxemia. Studies on the neurologic sequelae of paranatal asphyxia, and on cerebral injury in the newborn due to anoxia, have been made by Schreiber (242, 243), and Schreiber and Gates (244). Cole, Kimball and Daniels (48) discussed etiologic factors in neonatal asphyxia, and clinical observations of this condition were reported by Wilson, Torrey and Johnson (282). Windle and Becker (284, 285) studied experimental anoxia and asphyxia of the newborn, and Kabat (142) discussed problems ancillary to the neuropathology following arrest of the brain circulation in very young animals.

Schreiber, and Schreiber and Gates, described localized and generalized brain atrophy, medullary necrosis and a few ganglion cells showing homogenization and vacuolation of the cytoplasm and pyknosis and eccentricity of the nuclei, as well as microscopic areas of devastation and hemorrhage. It is stated that in all deaths from cerebral anoxia the microscopic lesions are identical, regardless of the cause of the oxygen deficiency in the cellular tissue or age of the subject. In over 500 children with brain defects, 70 per cent showed a history of asphyxia, but one wonders if the asphyxia is the cause or the effect of the brain depression in these cases. In a number of cases of mental deficiency and neurologic defects in children, it is presumed that the etiology is paranatal asphyxia, and that there is a definite relationship of fetal oxygen want and post-natal neurologic sequelae. However, much more than simple asphyxia may be involved in many of these cases.

Kabat (142) pointed out that statements have appeared in the literature, without any experimental basis, maintaining that the brain of the newborn is less resistant to anoxia than the adult brain. Schreiber (242-3), for example, was of the opinion that considerable clinical evidence supports the conclusion that the brain tissue of an infant can sustain much less oxygen deprivation than can the adult organ, and, therefore, is more readily damaged from this particular cause than is adult cerebral tissue. Kabat noted, however, that clinical observations on asphyxia neonatorum (Wilson, Torrey and Johnson, 282) reveal that the newborn infant can recover completely after severe asphyxia prolonged far beyond what would constitute fatal asphyxia in the adult. The great resistance of the respiratory center of the newborn is attested to by the prompt response of severely asphyxiated infants to lobeline. Kabat also found that newborn resistance to temporary arrest of the circulation of the brain surpassed that of the adult (pathologic findings to be published by Kabat and Grenell, 147).

Windle (283) has reviewed the studies on intrauterine respiration, respiratory changes at birth and tolerance by the newly born of anoxia. In 1912, Windle and Becker (281) studied the effects of anoxia at birth on the central nervous system of the guinea pig. The abdomen of the animal at or near term was anesthetized, with one cc. of a one per cent solution of procaine hydrochloride.

No other anesthetic was employed. One fetus was delivered immediately through a midline incision, to serve as a control. The uterine vessels were then clamped or the umbilical cords of the remaining fetuses were compressed through small incisions in the uterus. Varying degrees of anoxia were induced in 103 animals. Fifty-eight of them were delivered just before or just after intrauterine respiratory movements, induced by the anoxia, had ceased. Survivors (38 per cent) were those which suffered no anoxial apnea and required no resuscitation. Forty-five guinea pigs were delivered after 6 to 21 minutes of anoxia, after the fetal heart had become slow and often after it could no longer be palpated. Resuscitation was accomplished in 71 per cent of them by inflating the lungs with oxygen, or oxygen containing ten per cent carbon dioxide. Resuscitation was accomplished in a few minutes to more than an hour; the time required was not consistently related to the duration of anoxia. These animals exhibited characteristic symptoms of asphyxia pallida; namely, apnea, atonia, bradycardia, relaxation of anal sphincters, and cold, pale skin. The brains showed great variation in histological changes in 17 specimens compared with their normal litter-mates. Lesions were questionable or slight in six animals, subjected to less than eight minutes of anoxia. Definite, often marked changes were present in all others. Generalized necrosis of brain and spinal cord with chromatolysis, edema, small hemorrhages and ventricular enlargement appeared during the period from two to five days after birth. Glial proliferation and loss of nerve cells, especially in pyramidal layers of the cerebral cortex, was observed between five and nine days; and generalized atrophy, together with glial scars marked the older specimens (14 to 43 days). The most severe changes were not encountered in those specimens subjected to the longest periods of anoxia. The sites of damage varied widely from experiment to experiment. The authors noted that the nerve cells of the newly born appear to be much less vulnerable than those of the adult and withstand anoxia for greater lengths of time. There seemed to be less specificity in respect to 'anoxial' damage in the newborn than in the adult (Kabat and Grenell, 146).

In 1943, Windle and Becker (285) presented a more detailed report of these studies. The pathologic report, although extended, has not yet been completed. It must be pointed out that the investigations of these authors, although of great interest, cannot be considered as studies of the effects of anoxia alone—that is, of so-called anoxic anoxia. They have produced generalized circulatory arrest. The fetuses have been subjected to complete temporary removal of all factors essential for the maintenance of life, which normally cross the maternal-fetal placental barrier. This is no more a pure anoxia than are the studies in adult animals in which the brain circulation has been arrested, so that for varying periods of time there is not only a lack of oxygen, but also a destruction of the blood-tissue and tissue-blood equilibria, with resultant accumulation of metabolites and occurrence of other abnormal events. It may be true that the lack of oxygen is the most important factor, but at present even that would be an assumption.

2. *Delayed death following suicidal hangings*

Observations on the histopathological changes in the brain in cases of delayed death by suicidal hanging have been made by Deutsch (62), Salinger and Jacobsohn (227), Müller (203), Strauss (260), Scholz (240), Bingel and Hempel (27), Döring (64), Helwig (115), and Dublin and Brown (68). Salinger and Jacobsohn reviewed a large number of case reports and described a patient of their own in whom the pathological and physiological pictures show remarkable similarity to those resulting from experimental temporary arrest of the circulation. In seven cases described by Strauss, the patients showed periods of hyperexcitability with running movements and inarticulate vocalization. There was early extensor rigidity and opisthotonos with flexor rigidity and extrapyramidal signs developing later, followed by the return of cerebral function, but with disorientation and clouding of the consciousness. As seen in many experimental animals there were late cerebellar symptoms and eventual recovery. Müller, Scholz, Bingel and Hempel, and Döring also reported cerebral pathology almost identical with that observed in cerebral anemia. In reviewing the early literature, Döring called attention to the absence of cerebral lesions other than capillary hemorrhage in death immediately following strangulation. In a nineteen year old male dying 96 hours after suicidal hanging there were regressive glial changes, together with severe nerve cell damage. Many ganglion cells were missing in the third lamina of the cerebral cortex, and in some areas in which the ganglion cells were almost completely absent, many of the remaining cells showed dark, shrunken nuclei with homogeneously stained cytoplasm. Some of the large cells were swollen, and in the decolorized cytoplasm Nissl's small, ring-like structures were seen. Rarely, there were incrustations in the pericellular meshwork. In general, the picture was that of Spielmeyer's ischemic cell change, but pathologic changes comparable to Nissl's severe cell disease were also observed. Severe cell damage was also seen in the thalamus, globus pallidus, putamen and caudate nucleus as well as in the Purkinje cells of the cerebellum. The putamen especially showed marked cell loss as well as the presence of many 'ghost' cells. In the region of the internal capsule there was softening and necrosis. No changes were observed in the substantia nigra, oculomotor and red nuclei, the pons or the medulla.

In Helwig's case, a man of 54 who underwent a block dissection of the neck under local anesthesia, death in convulsions supervened approximately three hours after accidental choking. The microscopic findings presented a picture of ischemic degeneration, the most striking changes being in the ganglion cells of the cerebral cortex which revealed diffuse alterations in all regions studied. There were varying degrees of chromatolysis, and the cell contours were altered, some being shrunken, and triangular. Many nuclei were swollen and darkly stained, while some cells showed clear, pale perinuclear zones. Considerable cell shrinkage was seen in laminae V and VI of the frontal cortex. In the hippocampus there was no loss of cells in Sommer's sector, but fragmentation and loss of the Nissl granules were observed. In Bielschowsky preparations ex-

cessive deposits of silver were observed in many shrunken nuclei, and there was some coalescence and fragmentation of intracellular neurofibrillae. The nerve cell changes described in this case present unusual interest in that they appeared after a remarkably short survival time. Progressive and regressive changes in glial cells were observed with definite increase in the numbers of astrocytes, many of which contained bluish-green cytoplasmic granules which showed an affinity for Sudan stain. In the white matter there was occasional perivascular round-cell infiltration. Lipoid stains also gave evidence of the presence of fat in the capillary walls and in the cells of the pia-arachnoid.

Recently, Dublin and Brown (68) have called attention to extensive cerebral lesions in the case of a 38 year old male psychotic patient with chronic alcoholism, who died 80 hours after suicidal hanging with a necktie. In the cerebral cortex swelling, chromatolysis, vacuolation and pyknosis of the nerve cells were observed. Many large pyramidal cells were fragmented and stained poorly. There were large areas of porosity and edema in the white matter. In the white matter here and there, the axis cylinders were tortuous, beaded and fibrillated. There was perivascular necrosis as well as necrotic changes in the small vessels themselves, around many of which single layers of oligodendroglia and lymphocytes were observed. Satellitosis was evident around some of the degenerated nerve cells. The hippocampus was markedly affected, but the most severe lesions were seen in the basal ganglia, especially in the globus pallidus, where the nerve cells showed as dark purple, homogeneous masses. The neurofibrillae were lost, the cytoplasm was indistinguishable from the nuclei, while the nerve processes were poorly stained and varicose. The Purkinje cells of the cerebellum had virtually disappeared, and the cells of the dentate and olivary nuclei were severely swollen, poorly stained or pyknotic. The spinal cord and peripheral nerves were essentially normal. Similar lesions were seen in rabbits sacrificed three weeks after cervical compression for brief periods. In animals which succumbed immediately to experimental strangling for $4\frac{3}{4}$ minutes, no lesions could be found other than vascular congestion.

In 1938 Chornyak (47) published a series of observations on structural changes in the brains of monkeys and human beings, produced by oxygen deprivation, due to experimental and clinical pneumonia. Cultures of pneumococci were injected into the trachea of monkeys just below the cricoid cartilage. The animals were autopsied immediately after death or were killed in order to eliminate post-mortem changes. The microscopic studies of the brains clearly demonstrated the relationship between the extent of the pulmonary involvement and the severity and distribution of the damage in the central nervous system. The lesions were similar to those produced by atmospheres deficient in oxygen and by carbon monoxide asphyxia. There was the same remarkable difference in the degree of damage seen in the nerve cells in the same brain as was seen in animals killed by direct exposure to anoxia. The neurons in the supra-granular lamina of the cerebral cortex were the most susceptible to anoxemia incident to the experimental pneumonia. The damage throughout the thalamus and basal ganglia was likewise as severe as in experimental asphyxia. Throughout the

brain stem in pneumonia there was the same relative difference in the degree of damage between the somatic and visceral nuclei as is seen in experimental asphyxia. The larger multipolar cells (motor) which occur in the reticular formation, nuclei of the hypoglossal, abducens, trochlear and oculomotor nerves, showed relatively less severe damage than was seen in the sensory areas in the brain stem, visceral efferent nuclei (*e.g.*, vagus and ambiguus), and in the correlation centers. The vascular changes were hyperemia, stasis, edema and diapedesis and endothelial reaction. The neurons in the supra-granular lamina within the psycho-projection or association areas, were damaged early, and before the occurrence of irreversible changes in the blood vessels. They are the most vulnerable neurons to oxygen deprivation.

All of the human cases showed marked signs and symptoms of oxygen deprivation. In six of the cases there was extensive and acute pulmonary disease, one of cardiac failure on the basis of thyrotoxicosis, and one with death five days after a cessation of respiration for five minutes following a D and C operation under ether anesthesia. This latter case illustrates the importance of the rapidity with which the anoxemia occurs in determining the severity of the damage. It is noted that this case is very similar to that reported by Bodechtel (29) who also found extensive laminated loss of ganglion cells, especially in the supra-granular layers of the cerebral cortex in a patient who died fourteen hours after a "temporary heart failure" during narcosis.

The changes in the brain found in these cases were similar to those produced experimentally in dogs by atmospheres deficient in oxygen and by asphyxiation with carbon monoxide, and in monkeys by experimentally produced pneumonia.

The brains in all cases showed non-inflammatory degenerative lesions. The upper layers were the most affected. In the areas of the cortex which showed severe damage throughout the entire thickness, the more complete necrosis could still be found in the upper layers. The nerve cells in the supragranular layers showed extreme swelling, to the stage when the cytoplasm was simply a water-laden bag surrounding the nucleus. Soon after this stage the cell membrane disappeared, and although there was complete destruction of the cytoplasm in some cells, the nucleus persisted. It was frequently dechromatinized. The nerve cells in the deeper layers showed much less intracellular edema with varying degrees of dechromatinization. These cells showed most marked damage and necrosis where the structural changes in the blood vessels were the most severe. In these areas there was cell loss irrespective of the lamina and scattered irregularly throughout the gray matter. Most of the changes in these infarcted areas were those of the so-called ischemic type as described by Spielmeyer (249, 250): cell swelling, cell shrinkage, cell coagulation, cell liquefaction. These are considered as changes in the nucleus—plasma ratios which are part of the process of dechromatinization. The cell liquefaction in these ischemic foci was in most instances preceded by complete dechromatinization of all structures; cytoplasm, nucleus, and nucleolus, *i.e.*, the "shadow-form." The small cells in the basal ganglia, the cells of the thalamus, and the Purkinje cells showed uniformly the most marked damage (after the cells in the supragranular lamina).

Areas of softening due to infarction were also found throughout these subcortical structures. Sommer's sector showed necrosis in one case. There was a marked reaction of the glia cells. The astrocytes showed hyperplasia and hypertrophy. The astrocytic reaction as well as the occurrence of rod-cells was found in laminae I and II in areas in which there was much less damage to the deeper layers. The oligodendroglia showed marked hydropic degeneration. The microglia were changed into rod-cells especially in the areas of incomplete softening. The gitter cell stage was reached in only very rare instances in the medullary substance.

The changes in the blood vessels were of particular interest. There was marked stasis. In the pial vessels, the stasis was especially constant in the veins. Extreme dilatation of the blood vessels and stasis with edema and diapedesis was most marked in the subcortical tissue. Throughout the cortex the larger arteries were frequently distorted, partially collapsed and empty. The Virchow-Robin space was greatly enlarged around such a vessel. The capillary circulation was in some areas hyperemic and appeared as in an artificially injected specimen, and in other areas within the same brain the capillaries were collapsed, empty, with marked perivascular edema. Their endothelium was hypertrophied, stained more deeply, giving the vessels unusual prominence. Vascular proliferation was very extensive in one case. Vascular sprouting was found in the areas of necrosis and frequently in the first layer of the cortex and the molecular layer of the cerebellum. Occasionally an irregular mass of endothelial cells, starlike in arrangement, marked the site of the disintegration of the vessel wall, usually a very small vessel or capillary. Throughout all the cases, the endothelial hyperplasia was extremely marked. This was most marked in the veins, especially in those in the parenchyma, although it was also seen in the pial veins. In some instances the endothelial hyperplasia extended entirely across the lumen of the greatly dilated and distorted blood vessel.

Throughout the medullary substance there were also marked edema and areas of rarefaction with glial cell reaction around the blood vessels, especially those showing marked proliferation of the endothelium.

IV. ISCHEMIA

1. *Arrest of the circulation*

A great number of observations have been made upon the effects on nervous centers of suppression of the circulation. The effect of compression of the carotid arteries has been known from earliest times. The Assyrians compressed these vessels in young men to lessen the pain of circumcision, and the carotid arteries were referred to by the Greeks as the "soporales" because of a supposed relationship to sleep. Travelling magicians in the Middle Ages mystified their audiences by causing a goat to fall helpless as a result of discrete manual occlusion of the carotids. The earliest recorded experiments on animals, those of Steno in 1667 on fish (256), and of Swammerdam (262) on mammals, describe the effects of occlusion of the abdominal aorta. In 1756 Albrecht von Haller (105) repeated Steno's experiment and described the results in greater detail. Other studies

of this type, involving the spinal cord, were carried out by Ségalas d'Etchepare (73), Stannius (254), Brown-Séquard (34), Kussmaul and Tenner (160), du Bois-Reymond (31), Vulpian (275), and Schiffer (235). Chevreul in 1870 recorded the effects of manual occlusion of the abdominal aorta in the horse. Luchsinger (175) also ligated the subclavian arteries, as did S. Mayer (189), Ehrlich and Brieger (69), Singer (247), Spronck (253), Münzer and Wiener (204), Herter (118), Sarbó (229), Jatta (139) and Righetti (221). De Buck and de Moor (37) reviewed all pathological studies on anemia of the cord up to 1900.

Further experiments on cord anemia by ligation of vessels have been performed by Marinesco (184), Juliusberger (141), Ballet and Dutil (21) and Tureen (270, 271, 272). More recently, studies of spinal cord anemia by other techniques have been done by Van Harreveld and Marmont (107) and Kabat and Grenell (148). Investigations of this nature have been augmented by clinical cases of aortic obstruction, most of the literature concerning which has been summarized in the papers of Petitpierre (210a), Dragescu and Petrescu (65a), Schlesinger (235a) and Kahler (151a). An historical review of the clinical aspect of vascular occlusion of the cord may be found in a summary by Tureen in 1938 (271).

a. *Spinal cord.* In 1895 Lamy (161) produced ischemia of the spinal cord in twelve dogs by experimental embolism, and demonstrated hemorrhagic areas in the gray matter after seven days. Lamy (162) described three stages of the cord lesions following this procedure. At first in the initial ischemic stage there was profound injury to the cord neurons. A stage of red softening was also differentiated in which rupture of the blood vessels was observed. In a final stage phagocytic activity was noted, as evidenced by appearance of granular cells.

Evidence that the spinal cord boutons are susceptible to the effects of ischemia may be derived from studies carried out by Marinesco (183) who observed acute pathological changes in the boutons terminaux in a rabbit surviving 17 hours after permanent ligation of the abdominal aorta. They were described as diverse in form and volume and were illustrated as hypertrophied granular structures on the surface of the cell body and dendrites. In opposition to the hypothesis of selective sensitivity of the synapse to ischemia, Kabat and Schadowald (151) have found normal boutons terminaux on severely damaged Purkinje cells of the cerebellar cortex in dogs subjected to complete temporary arrest of the circulation of the brain. Marinesco's findings are now being reinvestigated and further experiments are in progress (Hoff and Grenell) in an attempt to throw light on the still unsettled question of synaptic sensitivity to ischemia.

De Buck and de Moor (37) state that Nissl's method of staining is the most sensitive and satisfactory for detecting early changes as a result of anemia (they eliminate work done before the time of Nissl as of uncertain histological value). The validity and interpretation of these cell changes has been discussed by Greenfield (96). De Buck and de Moor (37) note that an animal has to survive at least three hours after the beginning of the occlusion, even when the aorta is permanently ligated, or no lesions can be found. Concerning the duration

of time of ligation necessary to produce pathological changes, they observed an astonishing discrepancy in the reports of various authors:

Juliusberger	found changes		0.5 hrs. after ligation of 1 hr.
Sarbo	found changes		1.5 hrs. after ligation of 1 hr.
Munzer and Wiener	found changes		5 hrs. after ligation of 1 hr.
Rhigetti	found changes		6 hrs. after ligation of 1 hr.
Jatta	found changes		12 hrs. after ligation of 1 hr.
Spronck	found changes		24 hrs. after ligation of 1 hr.
Jatta	found changes	after	3 hrs. of permanent ligation
Marinesco	found changes	after	6 hrs. of permanent ligation
Righetti	found changes	after	36 hrs. of permanent ligation

Although no definite or proven explanation of these differences can be given, they might be at least partially explained on the basis of individual differences in collateral circulation, metabolic rate, etc.

De Buck and de Moor agree with most authors on the following points: Histological changes in nerve cells begin with chromatolysis, formation of a reticulum and later loss of affinity for staining. However, for a time the cell may be dark and somewhat homogeneous in its staining qualities. The cells atrophy rather than swell. The nucleus is usually more resistant than cytoplasm and does not disappear until late in the process of cellular disintegration. Marinesco described swelling of cells as the first change. Peripheral vacuolization emphasized by this author is found by de Buck and de Moor and others to be a rather infrequent occurrence. Jatta described central vacuolization, and Sarbo a homogeneous atrophy of the nucleus. Jatta observed fragmentation of the nuclei. Swelling, fragmentation, atrophy, fusion, etc. have all been described. A few observers have noted eccentric nuclei and extrusion of the nucleus from the cell. Satellitosis is only infrequently mentioned. De Buck and de Moor reported neuronophagia and a cellular infiltration, possibly of lymphocytes or some unknown wandering cells. They concluded that there are no characteristic histological changes associated with anemia.¹

b. Cerebrum. The earliest study of experimental cerebral anemia was that of Astley Cooper (49) carried out in 1836, who ligated the two carotids and two vertebrales in dogs. He noted that death did not follow immediately, and that spasms occurred before cessation of respiration. Kussmaul and Tenner (160) repeated this experiment and stated that it is impossible to revive the cerebrum after two or three minutes of ligation, but they did not use artificial respiration. Magendie and Poiseuille (181) reported similar experiments. During the remainder of the 19th century, ligation of the four main cerebral arteries was performed by many investigators, and the accompanying physiological changes were fairly well worked out, such as the importance of the medullary centers in the maintenance of life. Brown-Séquard (33) obtained similar results, also without artificial respiration. He was, however, able to revive the cerebrum

¹Our attention has been called to the work of B. Rexed (some observations on the effect of compression of short duration of the abdominal aorta in the rabbit. *Acta Psychiat. et Neurol.*, 1940, 15: 365-398), relating anemia to changes in cord function.

after seventeen minutes of arterial occlusion. Vulpian (275) made observations similar to those of Cooper. In 1878, Mayer (189) repeated the experiments of Cooper and Magendie with great care. He found that the vasomotor and respiratory centers lost their excitability later than other cerebral centers; they were able to resume function 10 to 15 minutes after circulation was restored. Hayem (112) says that in the rabbit, the cephalic circulation is not always suspended by ligation of the four cephalic trunks; in general, when these vessels are ligated for ten to eleven minutes, reestablishment of the circulation does not revive the functions of the cerebrum. Aducco (3) observed that in partial anemia of the cerebrum the excitability of the psychomotor centers is increased. Hering (117) stated that after ligation of the carotids and vertebrals not only the gray substance became inexcitable, but also the white substance.

In other experiments cerebral anemia was induced by decapitation. Legallois (165) was the first to state that life could be maintained in a head separated from the trunk by transfusing it with oxygenated blood as soon after decapitation as possible. Brown-Séquard (33) injected arterial blood into four cephalic arterial trunks of a decapitated dog. The transfusion took place ten minutes after cessation of all respiratory movement. He noted movements of the eyes and of the facial muscles, which seemed to be directed by the will. Other observers report less satisfactory results. Loyer (174) never saw consciousness return in heads of decapitated dogs even if blood was circulated three or four seconds after decapitation. According to Hayem and Barrier (113) manifestations of consciousness and voluntary control reappeared if the transfusion was given not later than ten seconds after decapitation. When they waited eight to ten minutes the transfusion only gave abortive respiratory effects; after twelve minutes the head remained inert.

Thus, the opinions of these early investigators vary considerably, especially concerning recovery of function after circulatory arrest. The oldest method of stopping blood flow, as used by Astley Cooper, Kussmaul and Tenner, etc. and later by Hill (121), and Andreyev (13), was incapable of yielding accurate information (as are some later methods) in great measure because the anemia was never total due to the existence of a collateral circulation. This collateral circulation may explain in part the differing results obtained in various experiments. The anemia was total in the decapitation experiments, but in these cases the situation is much more severe and complicated. The early method of ligation is of value chiefly in investigating the range of variation in collateral circulation to the brain in different species and individuals. Hill and others have shown that these anastomoses are so extensive in many animals, especially dogs, that they cannot be killed by permanent ligation of the innominate and left subclavian arteries. Hill has stated that horses and goats can be killed by ligation of the carotid arteries alone, but has presented no experimental evidence on this point. He found that one of three cats died after ligation of the four main cerebral vessels, and that monkeys reacted in about the same manner. He emphasized that the least trickle of blood can maintain the activity of nerve cells for a surprisingly long period. This observation has been

confirmed repeatedly by numerous investigators. Even stagnating blood about nerve cells prolongs their life. Ségalas de'Etchepare (73) and Batelli (21a) found that after ligation of the abdominal aorta the struggles of animals lasted longer when the vena cava had been tied than when it had not. Cannon and Burket (45) reported that ligatures carefully tied about the colon and stomach do not produce serious impairment of function in these organs even after seven hours, but when blood is squeezed out of them by pressure between glass plates, activity ceases after three hours, and definite changes occur in the nerve cells. The histological changes they found in the autonomic ganglia after three hours of anemia were as follows: (i) disappearance of cytoplasmic granules and diffuse staining, (ii) moderate connective tissue proliferation, (iii) somewhat eccentric nuclei, (iv) after three and a half hours of anemia practically all cells have disappeared and only scattered remnants remain, and (v) one and a half hours of anemia produce no histological changes.

Roberts (222) demonstrated that even after ligation of the four cerebral vessels some pressure is maintained in the circle of Willis. In addition, Brown (32) has shown that spinal vessels readily carry dyes to and from the brain. Even in experiments in which the contractions of the heart have been stopped, such as those of Boehm (30), Batelli (21a), Crile and Dolley (56) and Heymans *et al.* (120), a number of difficulties are encountered. While the blood flow in the brain is presumably stopped completely, all other organs are also rendered anemic. The organism thus has greater difficulty in restoring the neurons to normal because of simultaneous depression of the heart, kidneys, lungs, liver, etc. Furthermore, there is the additional difficulty of determining the exact moment of cessation of expulsion of the blood by the heart, as well as the total duration of anemia. Pike, Guthrie and Stewart (212) have pointed out that slight fibrillation of the heart may maintain a small amount of blood flow; moreover, one cannot be sure the heart has ceased to function except by direct inspection. This difficulty is also attested to by Winkelbauer (286) and Longheed, Janes and Hall (171). It undoubtedly accounts for the remarkable reports of recovery after hours of apparent death (Prus, 214).

The use of anesthetics as a means of inducing cardiac arrest, or the incidental use of anesthesia in the procedure may complicate results. Since Quastel and Wheatley (218) demonstrated inhibition of oxidation in brain slices by narcotics, there is abundant evidence that anesthetics and narcotics interfere with the oxidative mechanisms. Recently, Grant, Weinberger and Gibbon (94) studied the resistance of the cerebral neurons to lack of blood supply by clamping the pulmonary artery in cats for a short time, thus arresting the entire somatic circulation. While this method is superior to earlier techniques, it is subject to many of the same difficulties and the surgical procedure would appear to be rather formidable. Weinberger *et al.* (279), working with cats, produced temporary anemia by this same method. At the end of three minutes and ten seconds permanent and severe pathological changes were found in the cerebral cortex. Longer periods caused lesions in the Purkinje cells of the cerebellum and nerve cells in the basal ganglia. In their experiments circulatory

arrest for periods in the neighborhood of seven and one-half minutes caused complete destruction and liquefaction necrosis of the cerebral cortex. The motor and visual areas of the cortex sustained the earliest and most profound damage. The olfactory, orbital and temporal regions of the cortex were the least susceptible. Lamina I, and, to a lesser extent Lamina II, were the least vulnerable of the cortical layers, while laminae III and IV were the most severely affected. The lateral geniculate nucleus is the most vulnerable of the basal nuclei in the cat, followed in order of susceptibility by the hypothalamic nuclei, the thalamic nuclei, the globus pallidus and the caudate nucleus.

Extensive investigations have been carried out by the method of temporary occlusion of the innominate and the left subclavian arteries proximal to the origin of the vertebral arteries, in cats and dogs, by Pike, Guthrie and Stewart (212) and Gildea and Cobb (88). This method, as Gildea and Cobb pointed out, also fails to produce a complete anemia of the brain, since the ascending blood flow in the spinal arteries has not been interfered with. This factor is of utmost importance, since the anterior spinal artery is so large that the excitability of the cerebral motor cortex can be maintained by blood supplied by this artery alone (A. and B. Chauchard, 46). Since the blood flow remaining after occlusion of the chief cerebral arteries is quite variable from animal to animal, the severity of the brain damage resulting from a certain period of anemia is rendered relatively unpredictable. Other criticisms of this procedure are the variable depressant effect of the anesthesia and the necessity of surgical procedures at the time of the experiment.

These difficulties, however, do not invalidate results obtained, some of which have been confirmed in other experiments. Pike, Stewart and Guthrie found that the occlusion of the vessels, prolonged over 15 minutes, permanently abolished functional activity of the cerebral and medullary centers. In their series of ninety-three cats (212), five animals recovered completely after an occlusion period of seven minutes, only one after 15 minutes, and none after 20 minutes. They concluded that more than fifteen minutes of cerebral anemia results in death no matter what methods of resuscitation may be used. They reported the early and remote effects of cerebral anemia as follows: Immediately after occlusion of the innominate and left subclavian arteries in a cat, the nose and mucous membranes became pale, the animal stiffened out, and respiration increased in rate and then developed irregularities, and ceased entirely after thirty seconds to two minutes. Reflexes, including the corneal reflex, disappeared and the pupils dilated. The heart speeded up at first, and then, as the vagus center was affected, became temporarily slowed. The picture at the end of occlusion was an animal with widely dilated pupils, lax and sunken cornea, motionless eyelids, no tear secretion, bloodless mucosa of the nose and mouth, relaxed muscles, no voluntary respiratory movements and low blood pressure. The heart beat was slow and weak. The authors considered the immediate cessation of respiration as the most reliable indication of a complete occlusion. After the vessels were released, provided the occlusion period had not been too long, the mucous membranes immediately became pink and respi-

ration returned suddenly, usually within two to sixty minutes. Reflexes and normal intraocular tension returned more gradually. Convulsions occurred at any time from a few minutes to several days after restoration of the circulation. These seizures were described as beginning usually with extensor rigidity, quickly changing into a less regular type of tonic convulsions and then into the clonic type. The symptoms in different animals were also described, especially those in which the occlusion period was longer than eight minutes. Some developed a spastic gait; others became peculiar in their behavior, developing yowling spells, running fits or "dementia."

Gomez and Pike (91) reported the neuropathological changes in these animals, which may be summarized as follows: Pericellular lymph spaces are dilated two to three times the normal size. In animals allowed to recover completely, this space is reduced to normal size. In tissue taken during the period of the anemia, the spaces are reduced or not greater than normal. Cats killed a short time after restoration of circulation show swollen cells. It was impossible to differentiate readily between normal cells and cells of cats killed without return of circulation, or cells of animals that have recovered. Cats that die many hours after restoration of the circulation and following a prolonged period of anemia have cells which are shrunken, and irregular in outline; pericellular lymph spaces are relatively wider than normal. Two types of chromatin changes occur; the first in large pyramidal ganglion cells, where chromatin tends to be clumped and takes a diffuse blue stain; this often extends into the nucleus which loses its outline and can only be made out by the presence of a deeply staining nucleolus. With more advanced changes the chromatin is broken down into fine dustlike particles and finally it may not stain at all. The second type of change occurs in small pyramidal cells and consists of loss of affinity for staining and complete disappearance.

In animals in which the period of anemia is long (22 minutes) and the period of survival several hours, vacuolization of the cytoplasm occurs; the nucleus is displaced, but there is no evidence of extrusion from cells. Occasionally the nucleus was found to take a stain similar to that taken by the cytoplasm. No change was found in the nucleolus. A certain time must elapse after a period of occlusion before characteristic changes occur. Neuroglia cells show no abnormalities.

Neurons of different animals and of different areas in the same animals show variation in susceptibility to anemia. Small pyramidal cells are the most sensitive and often show decreased affinity for staining. Purkinje's cells are next in order of sensitiveness. They show diffuse chromatolysis after 13 minutes of anemia. The cells in the medulla are more resistant. Eight to 13 minutes of occlusion usually produce very slight lesions. Twenty to 30 minutes cause changes not compatible with life of animals. Neuroglia cells are unaffected. The cells of the cervical cord are described as next to the medulla in their capacity to endure anemia. Spinal ganglion cells are the most resistant of all.

Hill and Mott (122) made histological studies of brains of monkeys in which cerebral anemia had been produced by the Astley Cooper procedure. They

found, after permanent ligation, that changes in the cortical cells occur within ten minutes, which consist of slight swelling and chromatolysis. They mentioned no controls. In animals that die within 24 hours the cortical ganglion cells show diffuse staining, absence of Nissl bodies and 'coagulation necrosis.' When signs of recovery are evident at the end of 24 hours, the cortical cells of such animals are swollen, the nucleus enlarged and displaced, but with some differentiation in the chromatic and achromatic substance remaining. Mott pointed out that this indicates that only biophysical changes have taken place rather than biochemical, and therefore no permanent cessation of function of the cell has occurred. Hill and Mott (122)^f repeated these studies on cats. They reported that in cats that die within 24 hours there is loss of chromatin granules and diffuse staining in cortical cells. In cats that die after 24 hours, swollen vacuolated cells with large eccentric nuclei occur. Neurofibrils showed no swelling. They concluded that large psychomotor cells of the cortex were more resistant to anemia than small pyramidal cells.

Spielmeyer studied cerebral anemia, and in a summarizing paper (250) he described the usual lesions and mechanisms involved. He found pale areas in the cortex due to dropping out of nerve cells. The remaining cells, when examined under high power, were seen to be shrunken, homogeneous and pale, usually corresponding well with the ischemic cell degeneration described in his book (249). This type of cell change is not universal; other types may be found. The main types seen with Nissl stain are:

Cell swelling ('Schwellungsvorgänge', Nissl's 'akute Schwellung'): The cells show rounded corners and plump processes; many of these stain blue and are visible for a long distance; the chromidial substance is disintegrated, at least near the nucleus. The whole cell takes a diffuse blue stain, there being no unstained spaces.

Cell Shrinkage ('einfache Schrumpfungen', Nissl's 'chronischen Zellerkrankung'): The whole cell is shrunken and often elongated, including the processes. The chromidial substance stains darkly, is less in amount and may be in clumps. The spaces which normally are unstained take on color and largely disappear. The outline of the cell is angular, loses its round curves and where the processes come off there are sharp angles. The nucleus loses its roundness and may take on something of the shape of the cell; it is dark and the nucleolus may be larger than normal.

Cell Liquefaction ('Verflüssigungsprozesse'): The cells are pale and swollen, with rounded outlines, the chromidial substance disappears and rings of detritus often remain in the cell body; dark-staining granules and globules are seen, most often in the processes. The nucleus is round, small and metachromatic; the nucleolus is large, dark and near the edge. This is apparently a pernicious process, and all stages between the one described and complete disintegration are found; it was therefore called by Nissl 'schwere Zellveränderung'.

Cell Coagulation ('Gerinnungsvorgänge', 'Koagulationsnekrose'): The cell body is pale, apparently decolorized; it is shrunken, angular and unusually elongated. The processes are lost or difficult to see; they may be encrusted

with degeneration globules. No chromidial substance is seen, and the cytoplasm is almost colorless or bluish and homogeneous. The nucleus loses its rotundity and may be triangular or irregular; it is dark, often metachromatic, and the nucleolus is seen with difficulty; it is usually enlarged and at the edge. This type of change is found most frequently with vascular occlusion, and is called by Spielmeyer 'ischämische Zellveränderung'. Subspecies of this type are characterized especially by homogeneous change and impregnation with degeneration granules.

Alzheimer's Fibrillary Degeneration: This shows swollen, irregular cells with loss of chromidial substance, but special stains must be used, for the Nissl picture is not entirely characteristic. Pigment and fat changes: These are not well seen because of alcoholic fixation.

Buzzard and Greenfield (38) summarized the accepted results of cerebral anemia at that time, as follows: Partial interference with blood supply produces cellular changes similar to those due to various poisons. Sudden and complete cutting off of blood supply from any part of the central nervous system leads to rapid cell change characterized by reduction in the size of the cell body, the whole cell staining homogeneously with the basic dye. This has been illustrated by the results of experimental ligature of the carotid and vertebral arteries or of the abdominal aorta in animals, and by the result of thrombotic lesions in human brains. There is evidence to show that chromatolysis, together with some swelling of the cell and displacement of the nucleus, may be recovered from, if and when the circulation is reestablished, but the state of cell shrinkage associated with uniform deep staining indicates that a biochemical change in the protoplasm has taken place, from which recovery is impossible.

Gildea and Cobb (88) state that "anemia, if severe and prolonged enough, produces some form of lesion of the central nervous system; that fifteen minutes or less of practically complete anemia results in permanent loss of function of many cells of the medulla and the cortex and that histopathologic changes can be made out if an animal is kept alive a certain time after the period of anemia. Some observers report changes at the end of ten minutes, but the majority consider from one to three hours, or longer, necessary for the production of lesions. We find that almost every type of lesion has been described, but that perhaps the commonest type of cell change is the shrunken, homogeneous, dark-staining variety. Shrunken cells that have poor affinity for staining and a definite reticulum are also common. Satellitosis or glial proliferation are only infrequently mentioned. Chromatolysis is always mentioned, but apparently means different things to different observers. The variety of these observations makes it seem improbable that any type of histologic change can be described as pathognomonic." Their own varied experiments (88) have produced interesting results. They were fully aware of the incompleteness of the anemia. Their findings were:

Cerebral anemia, if sufficiently complete and prolonged, produces lesions that are demonstrable in sections of the cortex stained by Nissl's cresyl violet method. No one type of lesion can be said to be pathognomonic of cerebral

anemia. The most severe lesions consist in focal areas of necrosis. Shrunken, homogeneous and dark-staining cells predominate in the lesions of the majority of the cats, but swollen vacuolated cells are not infrequent. Focal areas of necrosis require at least twenty-four hours to appear, but shrinkage, chromatolysis and homogeneous staining of the cells appear immediately after a period of cerebral anemia which is sufficiently complete and prolonged to cause death. The size of perineural spaces does not seem to depend on severity of anemia, or on the length of time the animal lived after the period of anemia. Lesions are usually diffuse, but the most marked changes occur in laminae III and V. Large and small pyramidal cells appear more susceptible than other cerebral cells. Oligodendroglia cells show little or no swelling even in cats in which most of the nerve cells are abnormal. They state that periods of anemia of not more than ten minutes result in permanent injury to the cortex, and not uncommonly in changes which end in death from convulsions or failure of the respiratory center and that the occasional recovery of cats after an anemic period of fifteen minutes can readily be accounted for by the presence of unusually good anastomosis.

The most recent studies on arrest of the cephalic circulation are those of Kabat and Dennis (144), Dennis and Kabat (61), Kabat and Dennis (145), Kabat (142), Kabat, Dennis and Baker (143), Kabat and Schadowald (151), Kabat, Grenell and Baker (149, 150) and Kabat and Grenell (146, 147, 148). Although Pollock and Davis had devised a more delicate technique for cephalic circulatory arrest than those discussed above, their method (ligation of the basilar and carotid arteries under ether) still had the disadvantages of incomplete circulatory arrest and necessity of an anesthetic. Furthermore, in the dog and other animals the basilar artery is rather inaccessible. Kabat and Dennis (144) in 1938 devised a method by which they were able to obtain complete temporary arrest of the cerebral circulation without the use of anesthetics. This technique was as follows: "A preliminary surgical procedure is used, consisting in removal of both laminae and spine of the second cervical vertebra, and ligation of both vertebral arteries. After an interval of one to two weeks, the dog is given one to two mg. of atropine sulfate to prevent vagal cardiac inhibition, and placed, back down, on the table. A large blood-pressure cuff is wrapped around the neck, and the trachea intubated orally. By means of compressed air the cuff is rapidly inflated to a pressure of 350 mm. Hg. and maintained at this pressure. This procedure causes sudden complete anemia of the head, since not only the carotids and the cervical branches of the sub-clavians are occluded, but also the spinal vessels, by virtue of compression of the spinal cord." They go on to say that, "Sudden complete anemia of the head is followed by unconsciousness. There is a period of asphyxial activity and panting for a short time. After several minutes respiration stops, the animal becomes flaccid and the lid wink reflex disappears. As soon as respiration stops, rhythmic artificial respiration is begun through the tracheal cannula. The heart usually beats rapidly and vigorously throughout the procedure, but must be followed closely for signs of vagal inhibition. After a period of anemia

... the pressure is released. Artificial respiration is continued until the dog begins to breathe spontaneously. The lid wink returns some minutes later." These authors, in 1939, reported a modification of their technique with the following changes: (1) no ligation of the vertebral arteries, (2) Operation to arrest the circulation is performed two days after the laminectomy, (3) Pressure in the cuff is raised quickly to 700 mm. Hg. At this time they stated that, "The completeness of circulatory arrest in the head is determined by ophthalmoscopic examination of the retinal vessels. With this technic, consciousness is lost in a very few seconds, the corneal reflex disappears in from 20 to 40 seconds, and spontaneous respiration ceases in from 40 to 90 seconds." (This method is essentially that used in most of the present investigation. Additional new methods and developments, resultant symptoms and other points related to the technique will be discussed later.)

Kabat *et al.* have worked on different aspects of the problem under discussion with their new methods, and have reported an interesting series of results as follows:

1. If the arrest of the circulation was not longer than six minutes, there apparently was complete recovery of function, but stasis for eight minutes or longer resulted in permanent damage to the brain (Kabat, Dennis and Baker, 1941).

2. Young dogs were found to be much more resistant to acute cerebral anemia than adult animals (Kabat and Dennis, 145; Kabat, 142). Kabat (142) states that, "In the newborn, the respiratory center will apparently continue to function seventeen times as long as in the adult during complete arrest of blood flow in the brain. The ability of the newborn to achieve complete functional recovery following periods of complete arrest of the brain circulation is approximately 400 per cent greater than that of the adult. . . The resistance is diminished to the adult level at the age of four months." (It might be mentioned here that it has been known for a long time that young animals are considerably less susceptible to anoxia and asphyxia than adults. As early as 1725 Robert Boyle commented on the resistance of kittens to asphyxia, and Paul Bert in 1870 called attention to this fact. Since then many observers have reported similar findings, *e.g.*, Reiss and Haurowitz (220), Crile and Dolley (56), Andreyev (13), etc.)

3. A pregnant or lactating animal is more severely affected by stasis than the normal adult animal (Kabat, 142). Kabat remarked that, "... revival time is greatly decreased by pregnancy and lactation. This suggests the possibility that the greater susceptibility during pregnancy and lactation may be due, not to a difference in the rate of metabolism, but rather to a difference in the ability of the animal to overcome reversible neuronal damage." This latter statement, however, does not exclude effects of metabolic disturbances.

4. In severe cerebral anemia, Kabat and Grenell (146) have reported that microscopic examination of the brain showed well localized areas of destruction limited to the gray matter. In severely injured nuclei, complete disappearance of neurons and marked vascular and glial proliferation were observed. Most striking was the observation that these various nuclei appear to behave as units in resistance to anoxia. Characteristically, the severity of damage is remarkably uniform throughout a nucleus, and adjacent nuclei may show marked differences in susceptibility. This is emphasized by the fact that all pathological changes were perfectly symmetrical bilaterally. It is suggested that a group of neurons constituting an anatomical unit (nucleus) may also share specific metabolic characteristics.

Still another method of interrupting the blood flow to the nervous system in an intact animal is to produce general circulatory collapse and then to revive

the animal. Various means of producing circulatory failure have been employed: electrical shock to produce ventricular fibrillation, chloroform intoxication until the heart beat disappears, and exsanguination. Batelli (21a) produced ventricular fibrillation by electrical shock and then effected a return to the normal beat by cardiac massage and passage of an alternating current of 240 volts directly through the heart. The period of circulatory arrest was assumed to begin with the fibrillation and to end with the beginning of cardiac massage. He concluded that the limit of duration of cerebral anemia after which resuscitation was possible was in the neighborhood of fifteen minutes.

Crile and Dolley (56) chloroformed dogs and calculated that the period of circulatory arrest began when the first heart sound was no longer audible. The animals were resuscitated with an intra-arterial injection of physiological solution of sodium chloride and epinephrine, artificial respiration and extra-thoracic cardiac massage. The reappearance of heart sounds was taken to indicate reestablishment of the circulation. With this method an animal was restored to normal after as long as seven and one-half minutes of apparent death. These authors regarded ten minutes as the maximum period of circulatory arrest from which recovery was possible.

Winkelbauer (286) bled dogs until "clinical" death occurred, the criterion of which was cessation of heart sounds, respiration and pulse. At this time blood was rapidly injected, epinephrine given and artificial respiration started. The resumption of the heart beat was taken to indicate the end of the period of circulatory arrest. He succeeded in restoring an animal after a period of twenty-three and one-half minutes, during which the heart sounds were inaudible. However, if the period of apparent death was longer than five or six minutes the dogs suffered irreparable injury.

Evans and McEachern (72) note that, "...diverse late histological lesions found in the brain, after apparently unrelated insults...vascular occlusion, intracerebral hemorrhage and cerebral contusion and laceration...should not be looked upon as unrelated lesions, but as expressions of varying degrees of the same functional disturbance...an interference with normal cerebral circulation." On this basis they have suggested that there are two chief factors involved in the mechanism of cerebral scar formation: (1) the relative degree of anemia in the affected zone, and (2) the absence or presence of free blood in the cerebral tissues. Sudden, complete occlusion of a vessel was produced in a monkey. The typical lesion resulting was a large cyst, surrounded by a minimal zone of glial and connective tissue hypertrophy. It was concluded that sudden complete occlusion of a main cerebral arterial trunk leads to a massive zone of anoxemia in which necrosis occurs, to be followed by liquefaction and absorption. T. B. Rasmussen (219) ligated the cerebral arteries in the dog. He reviewed the literature on this subject and found in his own experiments that ligation of either the anterior or posterior cerebral arteries or of both on one side failed to produce evidence of ischemia. Clipping the middle cerebral artery produced infarcts. He explained this failure to produce ischemic effects on the basis of collateral circulation.

Campbell and Forster (44) have described the pathologic picture seen in their animals after occlusion of the anterior cerebral artery. The primary changes occurred in the cerebral cortex which presented focal infarction and necrosis as well as diffuse obscuring of cortical stratification with accompanying glial infiltration and cellular changes of various degrees. There was some demyelination of the white matter.

Lesions of another type seen clinically—resident for example in the course of the middle cerebral artery and characterized by abundant scar formation—are interpreted as a result of a partial reduction in blood supply in the distribution of the blood vessel concerned. The anemia may be severe enough to result in lost or severe damage to neurons, but of a degree adequate to stimulate glial and connective tissue hypertrophy. Escape of blood through vessel walls (diapedesis) may also play a rôle in such processes. Evans and McEachern also feel that the two factors stressed above are of significance in determining the late results of infectious processes and of developmental disturbances involving the brain. An important concept discussed in relation to these points is one maintaining that varying degrees of oxygen deprivation produce variable grades of cellular change in the different elements comprising the nervous system (we would amend this to include not only oxygen deprivation, but also that of other blood constituents). In severe anoxemia, the death of all cells, neuronal and supportive may be expected. In moderate grades of anemia neuronal life is impaired, but glial and connective tissue elements are caused to hypertrophy. In less severe grades, neuronal integrity may be impaired without the occurrence of demonstrable changes in the supportive elements.

A discussion of the problems and literature related to tissue damage from disease of cerebral blood vessels may be found in the papers of Putnam (215, 216) and Putnam and Alexander (217). The latter describe diffuse and local effects of total, partial, subacute and chronic general anoxia (from vessel closure), of asphyxia, and of specific syndromes resulting from vascular obstruction. They state that, "...the effects of obstruction of the cerebral circulation are extremely variable, but fall into certain fairly definite patterns. Cerebral vascular occlusion does not necessarily, nor even usually, give rise to complete parenchymal destruction and cyst formation, but may result in selective damage to certain tissue elements, notably the myelin and certain ganglion cells. Demineralization is a constant phenomenon. Our knowledge of the subject is obviously incomplete, but the list of neurological diseases in which vascular obstruction plays a part is constantly growing. It seems likely eventually to include most of those conditions which are not neoplastic, heredo-degenerative, suppurative or the result of vitamin deficiency, and even many which do fall in these categories."

Clinical observations have also shown a difference in the reactions produced when the capillary bed of an area is completely closed from that seen when it is only partially closed. Alexander and Woodhall (5) presented three cases of epilepsy, each due to a focal brain lesion. The lesions in two cases were traumatic; in one, presumably embolic in origin. Their findings were as follows:

1. The epileptogenic lesions in these three cases differed from the usual types of 'vascular' lesions (i.e., focal anoxic lesions caused by vascular occlusion or injury) only in the following two respects: (a) the lesions contained calcifications, and (b) the capillary bed of the involved areas was not completely destroyed, but merely reduced in density in two cases, partly reduced in density and partly distorted by varicose and sinusoidal dilatations in one case. Other lesions of a similar degree of gross necrosis and of similarly long standing show usually complete or almost complete destruction of the capillary bed.

2. The incompleteness of interference with blood supply is probably the cause of the calcifications in these cases. Without influx of calcium from the streaming blood, calcification of necrotic tissue cannot take place; since calcifications are formed by the combination of blood borne calcium with the phosphoric acid freed by the breakdown of lipid in necrotic tissue. Conversely, whenever enough calcium is brought into tissue undergoing lipid breakdown, calcification will inevitably take place.

3. The same basic mechanism is probably responsible for the calcifications in Sturge-Weber's disease, in other hemangiomatous tumors, in oligodendrogliomas, in Geyelin and Penfield's endarteritis calcificans cerebri, and in toxoplasmic encephalitis.

4. The abnormal blood supply of the epileptogenic foci is interpreted as being of possible importance in the elicitation of the epileptic discharges, in the light of the work of Gibbs, Lennox and Gibbs (87).

Summary. It has been pointed out that ischemia cannot be considered as equivalent to anoxia, although the brain lesions in each are similar. Anoxia is but one of the many factors ancillary to arrest of the circulation which contribute to the production of the observed central nervous system lesions. Of corresponding importance must be considered lack of all other substances necessary to maintain normal metabolism, as well as the accumulation of normal and abnormal metabolic end-products. The characteristics and distribution of the lesions may be determined in part by normal variations in blood supply and chemical composition of the several regions of the brain, including differences in concentration of such substances as creatine (Kerr, 156), ascorbic acid (Plaut and Bülow, 213), potassium (Tupikova and Gerard, 269) and glycogen (Zagani, 295). These variations would suggest that the susceptibility to anemia or ischemia may differ in the various regions of the brain. This postulate has been amply substantiated, and the evidence indicates that the so-called 'higher centers' are much more susceptible to lack of oxygen, etc., than are the lower centers. For example, Gellhorn and Spiesman (84) demonstrated in man that reflex nystagmus is unaffected by a degree of anoxia which greatly decreases the sensitivity of hearing (Gellhorn and Spiesman, 85) and of visual intensity discrimination (Gellhorn, 86). Lennox, Gibbs and Gibbs (167) reported that subjects of their anoxia experiments were all conscious when the venous blood leaving the brain was more than 30 per cent saturated with oxygen, but were all unconscious when the oxygen in the blood of the internal jugular vein fell below 24 per cent saturation. At the level of anoxia at which consciousness was lost, the lower centers continued to function, and cortical potentials, although greatly reduced in frequency, persisted. This concept of a gradient from higher to lower centers is supported by the observations of MacArthur and Jones (179) and Himwich and Fazekas (127) that there is a decrease in the metabolic rate as the neuraxis is descended from cerebral

cortex to spinal cord. A corresponding gradient in the vascularity was shown by Craigie (54, 55).

Although numerous reports since 1836 relative to central nervous system lesions subsequent to ischemia have considerably increased our knowledge, it was not until recently that the techniques employed to arrest the circulation were completely effective. This must be remembered in any consideration of earlier studies. The technical improvements have enabled observers to note that the cell changes are not merely scattered throughout the neuraxia, but often are definitely localized in certain areas. The typical cellular abnormalities are those of swelling, shrinkage, liquefaction, chromatolysis, coagulation (the ischemic cell change of Spielmeyer) and vacuolization. The lesions are confined to remarkably delimited areas. The neurons react with a constant degree of susceptibility or resistance, sensory cells being markedly more susceptible than motor cells and higher centers more than lower centers. The various nuclei behave as units in resistance to circulatory arrest, although adjacent nuclei may show marked differences in susceptibility. It is to be emphasized that cells appearing as an anatomical unit or nucleus may also share specific metabolic characteristics.

2. Acceleration

When the path of a plane at high speed is altered, as a result of inertia a centrifugal force is exerted on the pilot's body. This is known as the force of acceleration and is most easily expressed in multiples of normal gravitational force of 'g'. It is determined (Ham, 106) by the equation

$$F' \text{ (accel.)} = \frac{V^2}{32.2r}$$

in which V is velocity in feet per second and r is the radius of the turn in feet. When the force of acceleration is exerted from the pilot's head to his feet, it is called positive; the reverse is negative. Other types of acceleration exist which are dependent upon differences in position of the pilot's body.

The effects of acceleration such as that experienced by aviators on the central nervous system are being studied by many investigators, but the open literature as yet contains no reports of observed brain damage etiologically related to this factor. Firestone (77) maintained that high speeds will cause injury to the brain from its pressure against the skull. However, Bauer in discussing Firestone's theory, felt it more likely that a change in direction at high speed (as in banking a plane, etc.) might cause unconsciousness, and that actual brain damage might occur by the brain being sucked down towards the foramen magnum. Bauer stated that brain damage has been known to occur, but no evidence of this can be found in the literature.

Fulton and Thorner (80) discussed the possibilities of the production by acceleration of brain changes or of cerebral anemia, *i.e.*, whether the changes were the result of anoxia, of centrifugal changes of the brain, or of some combination of anoxia and other centrifugal effects. The recent detailed review of the liter-

ature and discussion of the effects of centrifugal acceleration by Ham (106) presents no further information, relative to nervous system lesions after positive, negative, transverse or other types of acceleration.

It is probable that whatever effects acceleration may exert on the central nervous system are the result of temporary cerebral ischemia. That acceleration will produce unconsciousness was noted by Erasmus Darwin, who, in 1794, mentioned the use by mill-wrights of the rotating mill-stone as a cure for insomnia.

V. CARBON MONOXIDE POISONING

The lesions described in the brain following carbon monoxide poisoning show many similarities to those which have been observed in anoxic anoxia, asphyxia and ischemia. Following death from carbon monoxide the brain is hyperemic and edematous and usually shows punctate hemorrhages (Mott, 201; Kammy, 152; etc.). Drinker (67) also called attention to nerve cell damage in the cerebral cortex, corpus striatum, dorsal vagal nuclei and other areas of the medulla.

Recognition of the harmful effects of carbon monoxide dates from the time of Erasistratus (ca. 300 B.C.) who assumed that dilution of the air by coal vapor was the principle factor, and that the resulting lack of air destroyed the tissues. Carbon monoxide poisoning was also discussed by Galen, Avicenna and Hoffman (129). Although Claude Bernard (24) appears to have been the first to discover that carbon monoxide displaces the oxygen in the oxyhemoglobin of the blood, it is claimed by Lewin (169) that Troja was the first to describe the cherry-red coloring, and that Pierry had called attention to it in 1826. Hoppe-Seyler also observed this phenomenon at about the same time as Bernard.

The theories held in regard to the pathological action of carbon monoxide by investigators up to the middle of the nineteenth century were divided by Klebs in 1865 into two main groups: one holding to the idea of death by suffocation (oxygen deficiency), the other considering carbon monoxide to be a true anesthetic on account of the similarity of many of the symptoms to those of an anesthetic such as opium. Klebs studied the changes in man and animals. He made the hypothesis that the dilatation of the cranial vessels, especially those of the cortex and the large brains, exerts pressure on the substance of the latter which causes the soporific condition. He thought that the grave nutritional disturbances caused by oxygen deficiency of the blood possess an important significance for the after effects and perhaps explain some of the manifold nervous disturbances that frequently remain behind after carbon monoxide intoxication. Haldane in 1895 stated that carbon monoxide, apart from its influence on hemoglobin, is a physiologically indifferent gas and that its poisonous action is entirely due to its power of combining with the hemoglobin of the red corpuscles, thus putting them out of action as oxygen carriers.

Since that time many investigations have been undertaken to clarify the biochemistry, physiology and pathologic anatomy in carbon monoxide poisoning. (The discussion here is restricted to those reporting nervous system lesions).

The opinions regarding the pathogenesis of the cerebral changes in carbon monoxide poisoning vary. Jakob (137), Gleister (89), Dreser (quoted by Meyer, 66), Mathews (187), and others favor the explanation of the direct action of the carbon monoxide itself on the brain tissue. Strecker, Taft and Willey (261), Henderson (116), Haldane (103), Beck (23), Walters (276), Haggard (102), and Yant, Chornyak, Schrenk, Patty and Sayers (293), etc., feel that anoxemia is mainly responsible for the changes in the brain. Sayers and Davenport (230), Hill and Semerak (123), Simon (quoted by Ruge, 1922), Photakis (211), Sibelius (246), Drinker (67) and others, emphasize the rôle played by the structural changes in the blood vessels in the development of the brain changes. Functional vascular disturbances were regarded as significant by Spielmeyer (251), Hiller (124), Grinker (100, 101), Weiman (278), Meyer (193, 194, 195), Hill and Semerak (123), Sayers and Davenport (230), Klebs (157), and others.

Stewart (257), Gordon, Taylor and Margolies (93), Delafield and Prudden (59), Grinker (100, 101), Ruge (225), Ferraro and Morrison (75), and Hsu and Ch'eng (134), among others, favor the combined influence of anoxemia and vascular damage. Novarro and Monakow and Kitabjaschi (200) emphasized the importance of the damage of the hematoencephalic barrier, i.e., the choroid plexus and the ependyma in the causation of the cerebral changes.

Many investigators have pointed out specifically that it is the so-called "softenings in the lenticular nucleus" that give to the cerebral findings the imprint characteristic of carbon monoxide poisoning. The predominance of the pathological changes in the globus pallidus is, according to Kolisko (159), and Goldstein (90), to be ascribed to the peculiarity of the blood supply of this structure. As the blood vessels branch here at right angles, circulatory disturbances occur readily in the globus pallidus especially because of the abnormal impact of the blood current. Eros and Priestman (71) concluded that, "cerebral changes in a case of carbon monoxide poisoning are interpreted as resulting from vascular disturbances which are first of a functional, and afterwards of a structural nature; these disturbances are known to be accompanied by various secondary mesodermal and parenchymatous reactions. The anoxemia is probably the initial local vascular factor which ushers in the functional vasospasm; the circulatory disturbance resulting from the subsequent vascular damage may in turn cause additional anoxemia."

Hiller (124), in a summary of the literature on the changes in the central nervous system after carbon monoxide poisoning, divided the studies into groups: one lays emphasis on the vascular changes as the cause of the definitely localized softenings, the other considers the softening as a kind of encephalitis. In still other investigations the softenings and thromboses are not referred to any vessels. According to Weimann (278), the softening in the pallidum and other cerebral regions (cortex, cornu ammonis, cerebellum) characteristic of carbon monoxide poisoning is not the result of direct injury of the nerve tissues by carbon monoxide, alteration of vascular walls or thrombotic closure of the vessels, but of disturbances of circulation. These are conditioned on a severe

functional injury to the cerebral vessels, above all a paralysis of the vaso-constrictors, which leads to a dilatation of the vessels, and an excess of blood in the vessels with retardation and stopping of the blood stream, through which the softenings originate as genuine encephalomalacia.

The most detailed analysis of nervous system lesions resulting from carbon monoxide poisoning is that of Yant, Chornyak, Schrenk, Patty, and Sayers (293). Their results are most important, especially in relation to the present investigation, because of their particular recognition of the differences in cell susceptibility. They may be summarized as follows:

1. The circulatory changes in the dog were characterized by dilatation, stasis involving the entire capillary system, and perivascular hemorrhages.

2. There is a marked difference in the susceptibility of the nerve cells to oxygen deprivation. The cells of the cortex, especially those in the outer granular layer, thalamus, sensory and correlation centers throughout the brain stem and the visceral efferent nuclei, are the most sensitive. The nucleus ruber, nuclei of the oculomotor, trochlear, abducens, and facial nerves, the large polygonal-shaped cells in the reticular formation and the anterior horn motor cells are the least susceptible in the dog.

3. The circulatory changes in the rat were limited mostly to the larger perforating cerebral vessels. There was no congestion in the meninges, and the capillaries throughout the cortex showed no remarkable changes.

4. There is a marked difference in the reaction of the nerve cells of the rat as compared with those of the dog. The cerebrum of the rat, with the exception of some large cells in the olfactory cortex and large polygonal-shaped cells in the nonolfactory cortex, showed no damage. The motor type of cells, which are least susceptible in the dog, are much more susceptible to oxygen deprivation in the rat.

5. There are two general types of degenerative changes in the nerve cells following asphyxia: some become shrunken and stain diffusely; others show varying degrees of chromatolysis.

6. There is a definite and remarkable difference in the susceptibility of nerve cells in the same brain and in the same type of cells in different species, as the dog and rat.

These general results are similar to those found by Chornyak (47) after 'anoxemia'. He, too, points out the differences in cell susceptibility not only from animal to animal, but from cell group to cell group within one experimental animal or human being. He mentions that, "The nerve cells having the highest metabolic rate and, therefore, the most vulnerable and susceptible to the stimulating action of decreased oxidation are first, the neurons in the supra-granular lamina of the association area and later the neurons in the deeper layers of the cerebral cortex; and then, the Purkinje cells, thalamus, small cells in the corpus striatum, sensory and correlation centers throughout the brain stem and the visceral efferent nuclei. The motor cells in the cortex, nucleus ruber (magnocellular), nuclei of the oculomotor, trochlear, abducens and facial nerves, the large polygonal-shaped cells in the reticular formation, and the anterior horn motor cells of the spinal cord are the least vulnerable to oxygen deprivation."

Zimmerman (297) is of the opinion that carbon monoxide in pure form will not give rise to brain lesions which will appear only after exposure to impurities (such as benzol, etc.) accompanying this gas. Of rats and rabbits exposed to both pure and impure carbon monoxide to the point of unconsciousness and

beyond, only those subjected to the impure gas showed brain lesions on examination. It is possible that a similar problem may arise in the study of the effects of anoxia, i.e., brain lesions may be produced not by pure anoxic anoxia alone, but by the association with it of other factors.

VI. ANESTHESIA

1. *Nitrous oxide*

There is abundant evidence that neuropathological lesions resembling those caused by anoxia and ischemia result from overdoses of anesthetics and narcotics. The investigators studying injury from nitrous oxide find that the severity of the pathological lesions in the brain increases with survival time. The lesions are localized and variable in distribution and degree of degeneration. Necrosis of the lenticular nucleus and especially of the globus pallidus is almost an invariable finding. In many cases the clinical symptomatology may be properly related to such lesions. Cases are described in which the brain at autopsy shows slight thickening of the arachnoid and flattening of the cortical convolutions, thinning of the cortex with relative increase of white matter, and bilateral subtotal destruction of the globus pallidus. There are usually no definite foci of necrosis in the cortex. Nerve cells show a rather advanced degree of lipoidal degeneration. Gliosis of the white matter has been described as well as chromatolysis of the Purkinje cells.

Lowenberg, Waggoner and Zbinden (172) described a case of temporary arrest during nitrous oxide anesthesia. The patient remained unconscious until death 60 hours later. At autopsy there were scattered petechial hemorrhages throughout the brain. The third, fifth and sixth cortical laminae were largely destroyed, and showed only a few degenerated neurons. There were also severe changes in the cortical myeloarchitecture. In the caudate nucleus and putamen the small neurons suffered severe damage while the large cells were better preserved. There was moderate reduction in the number of nerve cells in the globus pallidus, thalamus and hypothalamus, while in the midbrain, Corpora Luysii, geniculate bodies, red nuclei and central gray matter, moderate neuronal degeneration was observed without reduction in cells. The substantia nigra and pons were normal. In many areas of the cerebellum the Purkinje cells were destroyed, but the granular and molecular layers were intact. The nerve cell changes were of two types. Some were shrunken with pyknotic nuclei, while others were irregularly shaped or elongated with pale, homogeneous or slightly granular cytoplasm and deeply stained nuclei, designated as ischemic in type. There was a moderate glial response, the oligodendroglia being swollen and increased in number in the white matter. In further cases (Lowenberg, Waggoner and Zbinden, 172; Lowenberg and Zbinden, 173) of death after nitrous oxide administration during which respiration ceased for short periods of time, similar lesions were found. That these lesions were not due solely to cessation of respiration is evidenced by the fact that the picture of Nissl's severe degeneration was also observed (Lowenberg and Zbinden, 173) in the central nervous system following nitrous oxide death without intercurrent respiratory

failure. Lowenberg, Waggoner and Zbinden (172) note that neuropathological changes are to be expected only in patients surviving at least 24-36 hours after the anesthesia. However, Lowenberg and Zbinden (173) observed severe nerve cell degeneration in cases of post-anesthetic death as early as one hour and a quarter after administration.

In patients dying from nitrous oxide anesthesia, Courville (51) described zones of necrosis in the frontal and parietal regions of the cortex, with most profound involvement of the deeper layers. Grossly there was injection of pial and cortical vessels with some thickening of the arachnoid. Individual cells of the cortex were degenerated and there were areas of patchy necrosis or devastation such as described by Gildea and Cobb (88). Some nerve cells showed the sclerotic changes described by Spielmeyer and correspond with the shrunken homogeneous cells of Gildea and Cobb. The cell bodies were deeply stained and pyknotic, with large pericellular spaces and shrunken nuclei. The dendrites tended to be twisted and corkscrew-shaped, with varicosities. Silver preparations showed fragmentation and disintegration of the neurofibrillae. The author is uncertain as to whether this type of cell change indicates irreversible damage. The severe cell disease of Nissl and Spielmeyer, comparable to the swollen cell change of Gildea and Cobb (as well as of Grenell) was also observed. Some cell bodies were swollen and poorly stained with darkly stained, shrunken, elongated and often eccentric nuclei (ischemic cell changes of Spielmeyer). Occasional pigmentary atrophy or calcification of cells was also observed. In the lenticular nucleus there was diffuse softening of the gray matter and necrosis, and for the most part the cell changes were identical with those in the cortex. The Purkinje cells were shrunken, darkly stained and homogeneous and there were many ghost cells. In some cases the cytoplasm was more or less devoid of tigroid substance, and at times vacuolated. The nuclei were occasionally displaced or partially disintegrated. Nerve cells of the nuclei of the brain-stem appeared to be quite resistant. Nerve-fibers in areas of cortical necrosis showed varicosities, vacuole formation and sometimes broad, leaf-like expansions or bulbs. There were very active changes in the microglia, and acute swelling and proliferation of the oligodendroglia as well as proliferation and regression of astrocytes. In necrotic areas the neuroglia tended to regress acutely along with the other cellular elements. The perivascular spaces were enlarged and in some instances contained fatty deposits. Courville (52) observed lesions in the globus pallidus in cases with long survival periods. He concluded that nitrous oxide acts chiefly by reducing the amount of oxygen in the blood as well as by producing stagnation of the circulation (cardio-respiratory failure). The areas of focal necrosis were ascribed to local vasodilatation and stagnation.

Abbott and Courville (1) pointed out that in patients surviving only a day or two after nitrous oxide poisoning, only small groups degenerated, whereas with longer survival times, histologic changes were more marked, occurring in the form of isolated or fused foci of necrosis, or destruction of cortical laminae. Necrosis of the lenticular nucleus, particularly the globus pallidus, was almost

always, observed. Patients show a symptomatology resembling progressive lenticular degeneration, or Parkinsonism.

Courville, in his monograph on the untoward effects of nitrous oxide anesthesia (52), has described its clinical and pathological manifestations in great detail. He concluded that the cerebral lesions after nitrous oxide poisoning are asphyxial and not toxic in nature, and that they are similar to those produced either by temporary ligation of the vertebral and carotid arteries, or by exposure to the action of asphyxiant gases, or by reduction of the oxygen content of the inspired air. Histologically, it was found that the cerebral cortex is not uniformly or symmetrically involved. He is of the opinion that the degree and duration of the anoxemia determine the severity of the lesion. The cortical lesions are classified as to degree and probably in order of their development, as sclerosis of scattered pyramidal nerve cells, patchy necrosis, laminar cortical degeneration and, finally, subtotal degeneration of certain limited cortical areas. The earliest lesions occur about the pericellular and pericapillary spaces, suggesting that necrosis is a result of disturbance of respiratory exchange between the tissue fluids and the cellular elements. The astrocytes within the areas of focal necrosis become degenerated, while those at the margins of these areas are proliferated to form with the new blood vessels, a typical astro-vascular scar. All stages of microglial activity leading to the formation of compound granular corpuscles may be seen in the necrotic areas.

In a case surviving 16 months following nitrous oxide anesthesia, showing severe neurological symptoms throughout this period, similar severe degenerative changes in the central nervous system, including symmetrical, bilateral degeneration of the corpus striatum, were reported by O'Brien and Steegman (209). Steegman (255) reported the case of a young adult male dying 12 days after nitrous oxide-oxygen anesthetic, in which there was pseudo-laminar degeneration with loss of ganglion cells and glial proliferation in the cerebral cortex, with comparable changes in the basal ganglia.

2. Other anesthetics

Pathological lesions similar to those seen in nitrous oxide poisoning have been observed by Steegman (255) in the central nervous system of patients dying following administration of avertin in amylene hydrate and cyclopropane. The author calls attention to the striking similarity of these lesions to those of known ischemic or anoxic origin. It was noted that the longer the survival time, the more discrete was the localization of the lesions.

In an experimental study of the pathological effects of hypnotic drugs on the central nervous system of cats and monkeys, Mott, Woodhouse and Pickworth (202), found that large and repeated doses of sulphonal, trional, veronal, dial, luminal, soneryl and urethane produced chromatolysis and some nuclear and cytoplasmic changes in the Purkinje cells as well as in cells of the medulla, pons and spinal cord.

The pathological changes produced by medinal have been investigated experimentally by H. Hoff and O. Kanders (128) in dogs. These workers found

that repeated daily injections of the drug produced severe ganglion cell changes in the inferior olivary nuclei, characterized by chromatolysis and vacuolation and atrophy of the cytoplasm. The fiber tracts were found to be intact. No degenerative changes were found in the cerebral cortex or in the Purkinje cells of the cerebellum. Nakamura (205) has also reported ganglion cell changes in experimental medinal poisoning. In cases of suicidal medinal poisoning, Hartman (108, 109) demonstrated marked pericellular edema with granular degeneration of the Nissl substance.

In six dogs given sodium diethyl barbituric acid for three and one half years, Seevers and Tatum (245) observed chromatolysis, shrinkage and homogenization of cells throughout the cerebral cortex, basal ganglia and thalamus. Marked proliferation of the oligodendroglia and diffuse increase in microglia were noted. The authors call attention to the opinion expressed in the literature that the neuropathological lesions produced by the barbiturates are secondary to vascular changes, but they also believe that these drugs may be directly injurious to nerve cells.

That overdoses of barbital and soluble barbital result in acute changes in the central nervous system has been demonstrated by Hassin (111) in three human cases. The principle changes noted were aseptic meningitis with dilatation of the subarachnoid space, parenchymal edema and diffuse changes in the ganglion cells, consisting of swelling, occasional chromatolysis and neuronophagia.

Symmetrical necrosis of the globus pallidus has been reported in barbiturate poisoning by Gonzales, Vance and Helpert (92) and DeGroat (58).

Dogs poisoned with amytal (Hartman, 109) showed brain changes similar to those reported by Nakamura (205), namely marked vacuolation and degeneration of nerve cells with clumping of the Nissl substance.

Gebauer and Coleman (83) reported a clinical case of delayed death after cyclopropane anesthesia in which the brain changes were nearly identical with those following nitrous oxide poisoning.

Schnedorf, Lorhan and Orr (239) have reviewed the literature and discussed problems relative to the anoxic effects of anesthetics. A bibliography together with a discussion of the effects of nitrous oxide anesthesia may be found in Batten and Courville's paper which appeared in 1940.

VII. HYPOGLYCEMIA

It is quite evident from the foregoing summary of the literature that anoxic anoxia, asphyxia and anemic anoxia as well as carbon monoxide and anesthetics may produce grave organic changes in the cells of the central nervous system within a relatively short time. Sugar and Gerard have emphasized that while the lesions following abrupt ischemia are primarily due to anoxia, other important factors may contribute. Among these, hypoglycemia plays a significant rôle.

The literature on the subject of cerebral damage in hypoglycemia has been reviewed in great detail by Weil, Liebert and Heilbrunn (277), A. B. Baker (18,

19, 20) and by Lawrence, Meyer and Nevin (163). The structural changes observed are similar in both clinical and experimental material whether due to insulin shock, hypoglycemia secondary to neoplasm or functional over-activity of the islands of Langerhans, insulin shock therapy, or experimental hypoglycemia in animals. A large number of investigators have demonstrated conclusively that lesions of the central nervous system result from hypoglycemia produced in these various ways (Ehrmann and Jakoby, 70; Campbell and Macleod, 43; Pemberton, 210; Heimann-Trosien and Hirsch-Kauffmann, 114; Wilder *et al.*, 280; Dahl, 57; Joslin, 140; Wohlwill 290; Howland *et al.*, 131; Schereschewsky *et al.*, 234; McClenahan and Morris, 178; Anderson, 10; Membrez and Razdoljsky, 191; Smith and Seibel, 248; Best *et al.*, 26; Stief and Tokay, 258, 259; Terbruggen, 266; Terplan, 267; Bodechtel, 29; Wolf *et al.*, 291; Grayzel, 95; Schleussing and Schumacher, 236; Blau *et al.*, 28; de Morsier and Mozer, 199; Schmid, 237, 238; Tani, 263; Baker and Lufkin, 17; Leppien and Peters, 168; Salm, 228; Lemke, 166; Lindsay *et al.*, 170; Nicolajev, 207; Accornero, 2; Baker, 18, 19, 20; Cammermeyer, 39, 40; de Morsier and Bersot, 198; Döring, 65; Freed and Wofford, 79; Kastein, 153, 154; Kobler, 158; Malamud and Grosh 182; Moersch and Kernohan, 197; Scheller and Stroebe, 233; Weil *et al.*, 277; Appel, Alpers, Hastings, and Hughes, 14; Ferraro and Jervis, 74; Hassin, 111; Layne and Baker, 164; MacKeith and Meyer, 180; Sahs and Alexander, 226; Tannenberg, 264; Jansen and Waaler, 138; Winkelman and Moore, 287; Lawrence *et al.*, 163). These lesions consist of gross vascular changes, hemorrhage and softening in the meninges and the brain. There are widespread areas of necrosis of the cerebral cortex and other gray centers. These necrotic areas may become continuous in the cortex, but characteristically end more or less abruptly. (This sharp delineation between degenerated and relatively normal areas of tissue has also been observed after temporary complete arrest of the cerebral circulation; Kabat and Grenell, 146). The necrosis observed in hypoglycemia is characterized by degeneration and destruction of nerve cells and by varying degrees of microglial, macroglial and mesenchymal proliferation. In some cases, the lesions are so widespread that few normal cells are to be found. The upper laminae of the cortex are usually described as being more markedly affected than the deeper layers, although all cortical layers may be involved and in some instances there has been some predilection for laminae III and V. Cell changes were often observed in the Sommer's sector of Ammon's horn and the Purkinje cells of the cerebellum. Several workers have reported marked susceptibility of the small neurons in the putamen and caudate nucleus, with less severe changes in the large cells of these centers and the globus pallidus. The most common nerve cell changes described were Nissl's severe cell change and homogenizing and ischemic degeneration, as well as simple chromatolysis, Nissl's acute swelling and sclerosis. Swelling of the axis-cylinders and perivascular round-cell infiltration have also been reported.

Defective oxygenation of brain tissue has been generally regarded as the principal cause of the necrosis in hypoglycemia, and while the majority of the investigators consider this to arise from vasomotor disturbances such as vasoconstriction or vascular stasis, others have indicated intracellular anoxia or

nutritive deficiency as the underlying etiologic factor. The possibility that endothelial proliferation may be instrumental in producing the ischemic changes has been discussed by Meyer (195), MacKeith and Meyer (180), Weil, Liebert and Heilbrunn (277) and Ferraro and Jervis (74). Kastein (153, 154) and Leppien and Peters (168) ascribed a direct toxic effect to the action of insulin itself upon the neurons. Other workers have discounted the vascular theory altogether. Wohlwill, for example, regarded alkalosis and disturbances in water metabolism as the cause of the widespread nerve cell changes in his cases. Hassin and others have emphasized the importance of edema. Schmid in a discussion of the reversibility of the nerve cell changes suggested that the lesions were a result of excessive output of adrenalin in response to insulin injection.

Stief and Tokay (258, 259), Grayzel (95) and Tani (263) believed that no significant brain changes resulted unless convulsions had occurred, while Weil, Liebert and Heilbrunn (277) found no parallelism between the frequency of convulsions and the severity of brain lesions. However, they saw severe changes more frequently in animals receiving higher doses of insulin. Lawrence *et al.* (163) relate the changes which they observed with the duration of hypoglycemic coma. In epilepsy, where cortical necrosis is said to arise on a vascular basis, in status epilepticus (Scholz, 240) and in pertussis eclampsia (Husler and Spatz, 135), destruction of nerve-cells and homogenizing changes have been observed which are identical with those found in hypoglycemia, although usually less widespread.

The changes described by Bodechtel (29) in a man dying 14 hours after an operative procedure during which the heart was arrested for ten minutes, and in which continuous artificial respiration was given, were identical with severe hypoglycemic changes. The degenerative changes described in one of the cases of Lawrence *et al.*, were similar to those noted by Gamper and Stiefeler (81) in strangulation. The pathological changes in hypoglycemia have also been found to be similar to lesions produced by anoxic poisons such as carbon monoxide and cyanide as well as by ether. Lawrence *et al.* conclude that the hypoglycemic mechanism cannot properly be described as anoxia, since this latter term should be reserved for the failure of tissues to receive an adequate oxygen supply and should not apply to the absence of an oxidizable substrate.

It is of interest that similar lesions have been described after the use of insulin and cardiazol in the treatment of dementia precox (the literature related to this problem has been summarized by Cammermeyer, 40).

DISCUSSION

It has been pointed out that the brain changes produced by anoxia (to some degree), hypoglycemia, CO poisoning, anesthetics, circulatory arrest, etc., are remarkably alike. This similarity may be due to one or both of two factors. Either all these physiologically abnormal states produce the observed reactions by means of a common mechanism, or the brain neurons inevitably respond to various disturbances of their "milieu interne" in the same way,—perhaps following a gradient.

The possible "common mechanism" is, apparently, a complex one, composed

of both structural, i.e. vascular, and functional or metabolic factors. Many investigators have considered the selective vulnerability a consequence if not a proof of the presence of end-arteries. Scharrer's study of the opossum (231, 232) has disproved this theory. Despite the presence of end-arteries throughout the entire opossum brain, localized specificity of neuronal injury was still apparent after CO poisoning. However, a vascular factor may still be of consequence as a result of the difference, in various areas of the brain, in the number of capillaries as well as in the pattern of the capillary bed, or as a consequence of changes in the walls of the vessels. Nilges (208) in a study of the arteries of the mammalian cornu ammonis, observed a type of vascular distribution characteristic of that region and especially of Sommer's sector. That this latter region shows a high degree of susceptibility to injury, is well known. Nilges concludes that the rake-like pattern of the arterial branches to this region (in contrast to the more common dichotomous arrangement) may be an anatomic basis for its specificity of reaction.

The metabolic factors involved are much more complex, being in all probability the products of combined abnormalities of cellular metabolic rate (i.e. of the carbohydrate metabolism—cellular oxidative processes), as well as of the mechanism of anaerobic glycolysis, and other reactions of a physicochemical nature. The existence of these factors is made clear by experiments such as those of Howe and Bodian (132) in which poliomyelitis virus, even when injected directly into such regions as cortical area 17 or the lateral geniculate body, would not attack optic centers, although other cell groups, for which the virus had a specific affinity, would be destroyed.

Much of the evidence also supports the assumption of the presence of a gradient of reaction. Results of experimental cerebral ischemia make the gradient concept almost undeniable, but it cannot be traced too far without danger of inaccuracy, in the present state of our knowledge.

Obviously anoxia cannot be considered the only factor, or in some instances even the major factor, in the genesis of neuronal pathology in the conditions which have been discussed here. In many cases great difficulty has been encountered in attempting to produce a typical pathological picture in the central nervous system as a result of acute anoxia alone. Convincing clinical as well as experimental evidence points to the significant rôle played by a large group of morphological factors and physiological mechanisms acting singly or en masse. A major task for future investigators must be the clarification of the rôle of each of these factors as well as of their combined action.

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TICK PARALYSIS: A CRITICAL REVIEW

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INTRODUCTION

From time to time during the past fifty years and from widely scattered areas of the world there have been reported instances of a disease occurring in man and animals associated with the corporeal attachment of certain species of Ixodid ticks. This disease has been characterized by flaccid paralysis of the extremities and not infrequently by progression to death. It has been observed only sporadically in man, but at times has constituted a serious economic problem to sheep herders in this country and in South Africa. It has apparently been entirely distinct from the more commonly observed tick-borne rickettsioses and piroplasmoses. The purpose of this review is to define this disease as clearly as possible as a clinical entity, to evaluate the evidence bearing on its etiology and pathogenesis, and to point out possible future lines of investigation. It might be mentioned at the outset that few human cases have been reported in detail and that speculations about its cause have been divergent and frequently based on inadequate experimental evidence.

HISTORICAL

Under the date of December 9, 1824, William Hovell (1), who had been journeying with his friend Hume from Lake George to Port Phillip in the Australian bush, recorded that there existed in that area a "small insect called the tick, which buries itself in the flesh, and would in the end destroy either man or beast if not removed in time," but he recorded nothing more to indicate the manner in which this destruction might be accomplished. Some years later, in 1843, Backhouse (2) in *A Narrative of a Visit to the Australian Colonies*, referring to the neighborhood of Shoal Haven, a point about seventy-five miles south of where Sidney now stands, stated: "Among the enemies [of sheep] in these rich coast lands is the 'Wattle tick,' a hard flat insect, of a dark color, almost the tenth of an inch in diameter, and nearly circular in the body; it insinuates itself beneath the skin, and destroys, not only the sheep, but sometimes foals and calves. Paralysis of the hind quarters often precedes death in these cases."

In 1884 Bancroft (3) in Queensland described weakness of the hind legs of dogs and cats occurring two or three days after the attachment of ticks. Death of the animal followed, except occasionally when the tick was removed. Bancroft writes that "death appears to reside in the salivary secretions, as it does in sand flies. . . ." A decade later, Anderson-Stewart (4) in an anniversary address given before the Royal Society of New South Wales described weakness, convulsions, constipation, incontinence, and respiratory failure in dogs infested with ticks. He had collected a hundred such cases from correspondence with colleagues. It is clear that he was not aware of the occurrence of a similar clinical syndrome in man.

Probably the first clear description of tick paralysis is that of Malley in 1904 (5) from South Africa. For years the farmers of the Eastern Province of the Cape Colony had recognized paralysis in their sheep and its causal relation to a tick bite. The sheep would be found lying in the veld after the first frost in May to mid July. It was widely appreciated that removal of the ticks shortly after the sheep became ill would usually result in disappearance of symptoms and return to normal within a few hours. A year later Borthwick (6) described the same condition as it occurred in the Fish River Rand of the Cape Colony. It was attributed locally to *Ixodes pilosus*. Often these ticks were found on sheep which were not paralyzed, but they were invariably found on those that were. The sheep were frequently killed by jackals, but if not many of them recovered spontaneously within 48 hours. Borthwick tried unsuccessfully to induce the disease in sheep by inoculating normal animals with the blood of sheep which had become ill. Several sheep were autopsied, but no gross lesions were found.

In two comprehensive monographs on the relation of ticks to disease, one in 1899 (7) and the other in 1908 (8), G. H. F. Nuttall failed to mention tick paralysis.

The occurrence of the disease in man in North America was not recognized until 1912. In that year Todd (9) published a note on a survey he had conducted in an effort to determine whether a disease similar to Rocky Mountain spotted fever occurred in southern British Columbia. Two of the patients described in the answers to his questionnaire had paralytic symptoms associated with tick-bite. Todd (10) extended the scope of his survey and requested information from 210 physicians, seven of whom mentioned cases which appeared to have been tick paralysis. Todd (11) credits Temple with observing the first cases in the United States. Temple (12) described three personally observed cases, one he had diagnosed over the telephone, and several about which colleagues had consulted him. His earliest case occurred in 1898. At about the same time that Todd and Temple were publishing their papers Cleland (13) in Australia described a patient who probably had tick paralysis. This patient was a young female, age 13 months, who died with complete motor paralysis and respiratory failure. A tick was removed from the scalp behind her left ear shortly before death. Since these early papers, numerous case reports have appeared from North America and Australia, and claims have been made for cases in France and the Mediterranean area. There are certain constant differences between the American and Australian descriptions, as will be noted later, but in general they are similar.

Shortly after the disease was described and the importance of the tick demonstrated, attempts were made to produce it experimentally in animals. Earlier, Sabbatini (14) while working on the anticoagulating factor in the salivary secretions of *Ixodes ricinus* had observed paralysis in experimental animals following intravenous injections of the emulsified ticks. Hadwen in 1913 (15) found that he was able to induce paralysis easily by allowing *Dermacentor andersoni* adult females to attach themselves to young sheep. Indeed, he reported that in

numerous trials he had no failures, but he found guinea pigs refractory. In the same year Hadwen and Nuttall (16) in Cambridge, England, produced paralysis in the dog with ticks imported from British Columbia. They obtained no effect, however, on a jackal and a horse. Since these early trials numerous investigators in various parts of the world have worked on the problem with more or less success. Although it seems established beyond doubt that in sheep and dogs and possibly other animals, a condition very similar to tick paralysis in man can be produced by allowing certain species of ticks to feed on the subject animal, the mechanism by which this effect is produced is still far from established.

THE DISEASE IN MAN

Tick Paralysis in man has been reported from most of the north-western United States and from Georgia, South Carolina, and Long Island. It has been reported from British Columbia, eastern Australia, and possibly from Crete and Somalia.

In America: There are scarcely more than half a dozen complete and thorough case reports of the disease in the United States. These are briefly abstracted below.

Case 1: Barnett (18). The patient, a six year old female from Kingston, Idaho, was first seen on June 8, 1936. On the previous day she had complained of itching and burning of her fingers and toes, but seemed otherwise well, and spent a quiet night. On awakening the following morning and attempting to put on her slippers she complained of pain in her legs and found when she attempted to stand that she was quite weak. When examined there was pain to passive movements of the hands and feet. She walked with a broad base. There was a slow nystagmus to both right and left, but the pupils and fundi were normal. The cranial nerves were normal. Biceps and triceps reflexes were absent. Hoffman's sign was not present. The grip was diminished about 50%. There was weakness of the trunk muscles. The abdominal reflexes, knee and ankle jerks were absent. There was ataxia of all extremities, most marked in both legs. Sensation seemed unimpaired throughout. A large tick, about one and one half centimeters in size, was removed from the scalp but was not positively identified. Within 24 hours after the removal of the tick the patient was entirely well, and was discharged at the end of 48 hours. There was no residual paralysis.

This patient gave a history of more sensory involvement than is common. It is to be regretted that laboratory data were not obtained. In all probability the offending tick was *D. andersoni*, since this is the common tick of this area and the one which has been most often implicated.

Case 2: Gibbes (19). This patient, a married female of unstated age from Columbia, South Carolina, was taken ill in June, 1938, four days after inspecting some pigs. Her illness was announced by paraesthesiae of the lower extremities and was quickly followed by weakness of these extremities. Twenty-four hours later she was unable to walk and in addition noted paraesthesiae and weakness of her arms and hands. Her temperature on admission was 100°F. Physical examination demonstrated weakness of the legs, with absent knee, ankle, and abdominal reflexes. Her gait was ataxic. Babinski's sign was not present. The reflexes in the upper extremities were entirely normal. Symptoms slowly progressed for eight days, during which time she lost the reflexes in her arms. Her speech

became thick on the eighth day of her illness; on this day an engorged tick was discovered on the right occipital region and removed. This was identified as a "wood tick." Since the "wood tick", *D. andersoni*, does not exist in South Carolina, this was probably *D. variabilis*. The patient was entirely well forty-eight hours following removal of the tick.

The duration of illness is noteworthy here. Usually the disease has run its course in seventy-two hours. It is possible that this patient's age (she is recorded as being married) accounted for the duration of her illness. The almost immediate recovery following removal of the tick is characteristic.

Case 3: Robenow and Carroll (20). A 9 year old white female became ill on June 12, 1938, with weakness of her extremities and pain in her left thigh. When first seen seven days later she was found to have sustained a painless burn on her wrist. Upon admission she was acutely ill and had a temperature of 100.6°F. There was a flaccid paralysis of both legs with absent tendon reflexes. The arms showed weakness and asynergia, but biceps and triceps reflexes were present. Her speech was thick, but she had no dysphagia. The eyes showed a marked lateral and vertical nystagmus; pupillary responses were normal. The Romberg sign was present. A spinal fluid examination showed an initial pressure of 130 mm. of water. The fluid contained three cells per cu. mm. A Pandy test was negative and the protein content was 50 mg. per cent. Colloidal gold test, spinal fluid Wassermann, and culture were all negative. Red, white, and differential counts on the blood were normal. Wassermann, tuberculin, and Schick tests were negative. Shortly after admission two ticks were found attached on the scalp below the parietal region. These were removed and within a few hours marked improvement in muscle strength was apparent. Five days later a third female tick was found and removed, but the patient appeared nearly normal at this time. The three ticks were identified as *D. variabilis*; two were females, one of which was engorged.

Here again the relatively long period of illness and sensory changes are unusual.

Case 4: Amesse and Lyday (21). The patient, a 4 year old female was admitted to the Children's Hospital in Denver, Colorado, on June 12, 1939. Twelve days previously she had picnicked in the Poudre Canyon. Three days before admission she found that she was unable to walk when she attempted to get out of bed in the morning, but in about two hours she had recovered functional control of her legs, and continued to play for the rest of the day. The following morning she was again unable to use her legs, but otherwise was perfectly well. The day before admission she lost control of her arms and appeared drowsy. Early on the morning of admission she choked when attempting to swallow water. Later that day her respirations became labored. When first seen her temperature was 99.6°F., pulse 104, and respirations 19. Respiratory movements were jerky, shallow, irregular, and abdominal in type. There was a complete flaccid paralysis of both legs. Her fingers could be flexed and the right forearm could be moved slightly. Squeezing power in both hands was markedly diminished. All tendon reflexes and abdominal reflexes were absent. The sensory system was intact. A large tick, *D. andersoni*, well engorged and firmly attached, was found on the right occipital region, and there was some enlargement of the posterior cervical nodes on that side. Spinal fluid examination showed a sugar of 25 mg. per cent, 1 cell per cubic millimeter, and a total protein of 25 mg. per cent. The white blood count was 17,400, but this was normal on the following day. The urine was normal. The tick was removed and the patient was placed in a Drinker respirator. Three hours after removal of the tick she was able to move her thigh, and on the second hospital day respiration was regular and movement of arms and legs was normal. Dysphagia persisted for 28 hours following removal of the tick. Four days after admission she was able to walk with difficulty and seemed entirely recovered nine days after.

Case 5: Beach and Ravenel (22). A four year old white female was admitted June 12, 1941 to the Roper General Hospital in Charleston, South Carolina. The morning before admission she complained of malaise, weakness, and staggered when she walked. After an hour her symptoms disappeared, and she continued to feel well for the rest of the day. The morning of admission she complained of headache and weakness of her lower extremities and was sent to the hospital with a diagnosis of poliomyelitis. On admission her temperature was 99.8°F., pulse 124, and respirations 28. Blood pressure was 100/40. She was a poorly developed and poorly nourished child who walked with a staggering gait. The patellar reflexes were hypoactive and the ankle jerks absent. The spinal fluid examination showed no cells, a total protein of 55 mg. per cent, a sugar of 45 mg. per cent, chloride of 740 mg. per cent, and a negative colloidal gold, culture, and Wassermann. Red, white, and differential counts on the blood were normal. Blood determinations of urea, sugar, chloride, calcium, phosphorus, protein, albumin-globulin ratio, and agglutinations against Brucella, typhoid, paratyphoid and Proteus X19 were all normal. On the patient's second hospital day a partially engorged female *D. variabilis* was removed from her scalp. At the end of twelve days only slight ataxia remained, which disappeared within two weeks.

Case 6: De Sanctis and Saint 'Agnese (23). This three year old female from Huntington, Long Island, first appeared for examination on July 30, 1942, because of fatigue and inability to stand. Symptoms began forty-eight hours before admission, but disappeared 24 hours later, and then recurred and progressed until admission. When first seen she did not appear acutely ill and had a rectal temperature of 98.6°F. Neurological examination revealed an ataxic gait, a Romberg sign, normal abdominal reflexes, absent tendon jerks in all extremities, and a doubtful Babinski sign on the right. The spinal fluid showed 10 lymphocytes per cubic millimeter, 48.1 mg. per cent protein, 54 mg. per cent sugar, and a negative smear and culture. Blood count, urine, and sedimentation rate were normal. A partially engorged gravid *D. variabilis* was discovered on the occiput the seventh day after admission. During hospitalization, and before discovery of the tick, paralytic signs varied slightly from day to day, but recovery was complete within forty-eight hours after removal of the tick. This patient pursued a benign course. De Sanctis and Saint 'Agnese thought that this might be due to a difference between *D. andersoni* and *D. variabilis*. Case 2 above, which also pursued a relatively benign course, was probably associated with *D. variabilis*.

From these case reports and from the fairly numerous brief reports it is possible to give what is probably a reasonably accurate clinical picture of the disease. The patient, usually a young female whose long hair conceals a tick, is perfectly well before retiring the evening prior to onset of symptoms but notices upon arising the following morning that her legs are weak. Locomotion is possible at this stage, and temporary recovery or progression of the disease may occur from this point. With the loss of locomotion, there is a rapid progression of ascending paralysis during the next twenty-four to forty-eight hours to a point at which the patient is unable to move either arms or legs and lies quite helplessly in bed. Sphincter function may or may not be retained. Except for possible apprehension the patient appears quite well. There may be vertigo or numbness and paraesthesias of the extremities. Rarely does the temperature exceed 100°F. until the terminal stage. Vomiting is occasionally observed. Stiffness of the extremities, restlessness, fatigue, aching legs, and photophobia may be complained of. The beginning of respiratory distress may occur quite suddenly and unexpectedly; when it does it usually leads to a fatal termination. Death may be preceded by convulsions. The mechanism of death is respiratory

paralysis. Ascending paralysis with bulbar involvement followed by death characterizes the typical course of the disease unless the tick is found and removed. Indeed, no case is reported where the patient recovered and a tick was found after recovery. Usually, if the tick is removed there is noteworthy improvement within a few hours. If breathing has been labored it becomes free, and muscular power returns. At times ability to walk is regained in a matter of twelve hours, and almost always within two days. Complete recovery within a week is the rule. In this country, unless the tick was found when the patient was in extremis, recovery has been invariable. There are almost no reports of permanent disability, although Mail and Gregson (17) reported one suggestive case with permanent weakness of the facial muscles and arms. The authors did not see the patient at the time of her original illness twelve years before, but pointed out that this might have been the result of an old poliomyelitis.

Objective findings throughout the illness are relatively few. The pulse and respirations are not elevated until bulbar signs supervene. The patient's appearance is usually quite normal except for apprehensiveness, although mental cloudiness or stupor may be present. The striking feature of this disease is ascending paralysis. Reflexes are diminished or absent. There may be apparent asynergia and dysmetria, doubtless the result of weakness rather than of cerebellar involvement. The onset of bulbar involvement is suggested by labored breathing, dysarthria and dysphagia. Paralysis of the extraocular muscles may occur. The pupil usually reacts normally to light and on accommodation, but may be somewhat dilated and fixed, particularly if respiratory distress progresses. If recovery occurs it is marked by gradual regression of the signs mentioned above and return of normal reflexes within forty-eight hours. Sensory changes are rare. One patient is reported to have burned himself unwittingly early in the paralytic stage of his illness. The special senses are not involved, although occasionally vertigo is mentioned. With cranial nerve involvement diplopia is common.

In addition to the six case reports already given many others have been reported more briefly. Todd (10) collected 11 cases from 7 physicians with whom he corresponded. All of these patients were children, the majority females, and all occurred in southern British Columbia. Five of the 11 patients died, three in convulsions. Most of Todd's correspondents reported that among those patients who did not die recovery was complete within 36 hours. In fatal cases the tick was invariably present on the head or neck at the time of death. Although precise entomological classification was not reported, the offending tick was probably *D. andersoni*. Later Todd (24) reported 10 additional cases collected through correspondence with colleagues in British Columbia and Montana. Only one of this group died, and it seems quite likely that this and one other who recovered had Rocky Mountain spotted fever, although from the brevity of the report it is impossible to be certain. All were under nine years of age except one who was a man of forty. Ticks were found on all these patients. The pattern of the disease was remarkably similar in all cases. Some

had a slightly elevated temperature. Each patient improved markedly within 24 hours after removal of the tick, and all were entirely well within a week.

In 1912 Temple (12) published three cases which he observed and several others which had been brought to his attention through correspondence with colleagues in Oregon and Washington. His first case was a five year old female who was unable to stand when she awakened one morning. That evening the patient's mother removed a tick from the child's head and on the following day the child was entirely well. His second case was quite similar: A six year old female had been ill for two days with a flaccid paralysis of all four extremities, and in addition had had aphonia, dysphagia, and labored breathing for several hours. Two ticks were discovered on the child's skin and removed. The following morning the patient was much improved, and was entirely well within a week. The third patient, a ten year old female with a complete flaccid paralysis, was well the day following removal of the tick. Temple did not see his fourth case. This patient's father described by telephone the child's inability to stand, and following instruction to look for ticks, found several. The patient improved rapidly. Temple mentions nine other cases from Oregon which he did not see personally. Two of these were characterized by high fever and rash, and were probably spotted fever. The remaining were similar to Todd's cases. One patient, a seven year old male, presented an ataxic gait and paralysis of the extra-ocular muscles. A tick was removed from his neck, but he grew worse during the next few hours, and required six weeks for complete recovery. Two patients died, but there is no record of post-mortem examination. It is extremely difficult to evaluate these case reports because of their brevity. Temple believed that the disease was entirely motor and that it probably produced no permanent changes in the brain or cord, but he cites no evidence other than clinical to support this view.

In 1916 McCaffrey (25) reported a patient from Princeton, B. C., an eleven year old female who during a seven day period developed progressive flaccid paralysis, incontinence, dysphagia, and respiratory distress. When first seen, breathing was labored. Temperature varied from 99.6° to 95.6°F. The pupils were dilated and failed to react to light. Tendon jerks were absent. On the seventh day a tick was removed from the occipital region of her head; in a few hours she showed marked improvement, and in three days was walking. The tick was identified as a half engorged female *D. venustis*, (now called *D. andersoni*). McCaffrey mentioned that similar cases had been seen in the Similkameen Valley some miles distant.

In quoting a letter from a colleague, Todd (24) reports the only case in which *Haemaphysalis cinnabarina* has been associated with paralytic symptoms. The patient, a ten year old female, developed paralysis of the lower extremities, absent patellar reflexes and "choreic movements." The following day her abdominal muscles were flaccid, and on the third day she was unable to move her arms. A tick was found on the scalp and removed. Shortly thereafter she developed respiratory distress, and died the following morning.

In the cases reported in the United States and Canada it has been most un-

usual for death to occur following removal of the tick. McCornack (26) mentions one such case in which death occurred from "bulbar paralysis" fourteen hours after an engorged wood tick was removed from the scalp. The patient, a five year old female from Libby, Montana, had had respiratory difficulty for a day and had been unable to stand for two. When first seen, stupor, complete flaccid paralysis, dysphagia, and inability to talk were noted. McCornack observed seven other cases which he thought to be tick paralysis, the majority of which were young females. One case, a twenty-two year old woman from Hillyard, Washington, was seen in 1903 for weakness and inability to stand for three weeks. Recovery in "a few days" followed removal of a large tick from her coccygeal region. Two of McCornack's patients complained of vague pains in the legs and feet when they attempted to stand. The majority of those who recovered were entirely well within a day or two after removal of the tick. One patient had weakness of one arm two years later. The offending tick was not always identified, but was probably *D. andersoni*. Several times ticks were found in funeral parlors on bodies of patients who had died of vague paralytic illnesses. A similar occurrence was mentioned by MacArthur (27) from British Columbia.

An instance of remarkably rapid recovery from severe paralytic symptoms was reported by Jeffrey (28) in a ten year old boy from southern Wyoming. For three days this patient noted progressive weakness until he was unable to lift his legs or his head from the bed. He complained of double vision. There was ptosis of the left upper eyelid and drooping of the angles of the mouth. Tendon and abdominal reflexes were absent. On the fourth day a tick was removed from his back, and within three hours improvement was far advanced. He was walking quite normally the next day. Two days later the boy was entirely well.

Gregson (17) found one hundred and fifty cases of human tick paralysis listed in the files of the Dominion Entomological Branch Laboratory at Kamloops, B.C. He reported twenty-seven of these in outline. All were from various districts of southern British Columbia. Twelve of the twenty-seven cases were females. Eight of his series were adults, and ten were less than the age of five; the youngest was three and a half and the oldest seventy-six. Most of the ticks were found on the scalp, but several were found on the vulva, the umbilicus, the axilla, and elsewhere. There were five deaths in the group, one of which had a spinal fluid examination done shortly before death. This fluid showed 290 leucocytes and a negative Pandy test. An unusual case occurred in a young female who underwent a mastoid operation three days after a tick had been removed from the back of her head. Following the operation she developed a flaccid paralysis. It was found that the head of the tick had not been removed. Its removal was followed by prompt disappearance of symptoms.

Mulherin (29) reported a seven year old female from Augusta, Georgia who complained of irritability, fatigue, vertigo, and paraesthesias of the hands and fingers for the twenty-four hours preceding admission. Ataxia, incoordination of the arms, absent knee jerks, and a Romberg sign were present on admission.

A half engorged female *D. variabilis* was removed from the scalp at this time, and within 9 hours the patient's patellar reflexes had returned and she was able to walk without falling. The author reported that the negroes of south Georgia were familiar with this picture and that when such symptoms occurred they would look for ticks.

Townsend and Nash (30) report an interesting case in which the patient's landlord's police dog developed paralysis of the hind quarters the day following the patient's death. Ticks were found on the dog and removed with recovery of the animal. The patient, a negro girl of four, had developed inability to walk and slight abdominal pain the day before admission. When first seen there was complete flaccid paralysis of the lower extremities, weakness of the erector spini muscle group and muscles of the upper extremities. Two days later there was complete flaccid paralysis of all extremities and evidence of respiratory embarrassment. On this day a tick was found on the scalp and removed, but the patient died two hours later.

Bassoe (31) described the case of a 49 year old college professor who was visiting the Rocky Mountain National Park. This man felt perfectly well on the morning of the onset of his illness, but in the afternoon noticed numbness and prickling of his fingers and an unsteady gait. The following day he was worse. Diplopia developed. On the third day he was incontinent of feces and developed urinary retention, dysphagia, and dyspnea. Following discovery and removal from his groin of a tick identified as *D. andersoni* he improved rapidly. Within several days he was entirely asymptomatic, aside from undue fatigue on walking.

Newton's patient (32), a 4 year old girl first noticed weakness of her legs ten days following a picnic in the woods. The next day she was drowsy and unable to walk. By the third day she could not swallow and was having respiratory distress. A large wood tick was found behind her right ear on admission to the hospital. This was removed and the child was placed in a Drinker respirator. The following morning respirations were normal and dysphagia had vanished. Three days later she was entirely well.

Recently Harper (68) briefly described a four year old negroess who had had a complete paralysis of her lower limbs for several hours. Her temperature was normal and her knee and ankle jerks were absent. On the following day a tick was removed from her scalp. Twenty-four hours later she was entirely well.

In Australia: Twenty-two cases of tick paralysis have been reported from Australia, but in several the diagnosis is questionable. The Australian disease differs from that reported from North America in the following respects: The patients appear more acutely ill; the height of the disease is not reached until 48 hours after the tick has been removed; *Ixodes holocyclus* is always the offending tick; recovery may require weeks; bizarre signs and symptoms are more common. Hamilton (33) has emphasized local paralysis as a feature of the disease.

A fatal case, the first appearing in the Australian literature, is described by

Cleland (13) in a 13 month old female. Progressive restlessness, weakness, flaccid paralysis, and dyspnea continued to death from respiratory failure despite the removal of a tick from the right mastoid region on the second day of her illness.

In 1924 Ferguson (34) reported a series of six fatal cases gathered through correspondence with physicians of Sydney and environs. One case was a male of sixteen months, who had been eating poorly for a month and was unable to walk the day before admission. On admission there was stridor, a normal temperature, and a pulse of 160. The pupils were dilated but reactive to light. Paralysis of the tongue and masseters with weakness of all extremities was present. A replete female *I. holocyclus* was removed from the scalp a half hour before death, two days after admission. The majority of Ferguson's six fatal cases had ticks removed before death. One patient exhibited "cardiac weakness."

Sinclair (35) describes a patient in whom death occurred even though the tick was removed early in the illness. This patient, a three and a half year old female with bronchial asthma, developed irritability, malaise, ataxia, and pupillary dilatation. A tick was found attached over the left parietal region. It was broken in removal but the remainder was excised immediately. Within 24 hours following removal, complete flaccid paralysis of all extremities, absent reflexia, incontinence, and paralysis of deglutition musculature appeared. Death occurred approximately forty hours after removal of the tick.

Hamilton (33), who rightly points out that tick paralysis is a dangerous disease in children in regions where ticks abound, describes a two month old infant first seen with extreme weakness. A tick had been present on the breast for at least three weeks. No knee or abdominal reflexes were obtained. The tick was immediately removed and the patient was given ten cubic centimeters of an anti-tick dog serum, a serum prepared by the Commonwealth Serum Laboratories from dogs on whom *I. holocyclus* had been allowed to feed, but the following morning the temperature was 103°F, the respirations 40, and death occurred shortly after the onset of cyanosis and respiratory difficulty.

The protracted nature of the disease as it occurs in Australia is illustrated by Hamilton's reports. A seven year old male removed a two-thirds replete *I. holocyclus* from the scalp behind his right ear several hours after the onset of photophobia. Later that day he developed an unsteady gait and diplopia. The following day dysphagia, dyspnea, flaccid paralysis, and areflexia appeared. He was given ten cubic centimeters of the anti-tick dog serum. Twenty-four hours later he was somewhat improved, although at the end of five weeks he still walked unsteadily. A second patient, 21 months old, was noticed to walk unsteadily. The following day the child brought its mother a large replete tick which she had removed from her body; at this time the gait was more ataxic, with frequent falling. She was admitted to the hospital 24 hours later, unable to walk, and with flaccidity of both legs. Knee and ankle jerks were absent; the abdominal reflexes were barely obtained. A spinal fluid examination showed normal pressure, protein and sugar. A Pandy test was negative. On

the fourth day of her illness, she was given vitamin B and ten cubic centimeters of canine anti-tick serum, and because of respiratory difficulty was placed in a respirator. Dysphagia was marked. Improvement began on the sixth day of her illness, but an intercurrent scarlet fever delayed recovery. Return of muscular power was very gradual.

Uncommon sites of tick attachment are illustrated in Strickland's (36) and Moss' (37) reports: The former reports a case of tick paralysis in his son in whom the tick lodged in the external ear. Lower extremity paralysis disappeared 10 days following removal of the tick. Moss cites a 35 year old female who complained of inability to read, blurring vision, weakness, sharp pains in both legs, and a small vulvar abscess. No other neurological findings are mentioned, but the abscess proved to be a deeply embedded *I. holocyclus* with surrounding suppuration. It was excised, and normal vision returned in two days. The leg pains gradually abated and the weakness disappeared.

Facial paralysis resulting from tick bite is illustrated in Foster's (38) case in which the tick lodged in the left external auditory canal with subsequent left facial paralysis, and in Crossle's (39) case in which the tick again was discovered in the external auditory canal of the side showing facial paralysis.

Ptosis of the right eyelid reported by Hamilton (33) disappeared following removal of a tick from the right temple. The same author describes right arm weakness and wrist drop in a second patient which cleared following removal of a tick from the right axilla.

Bancroft in 1884 (3) described inability to read small print, weakness and vertigo in a 40 year old female, all of which disappeared following removal of a tick attached near the ear.

The importance of removing the entire tick from the skin and subcutaneous tissues is illustrated by Eaton's case (40). This four and a half year old female developed restlessness, anorexia, and unsteady gait. A tick embedded in the right scapular region was partially removed, the mouth parts remaining. Twenty-four hours later there was flaccid paralysis of the lower extremity, weakness of the arms, and absent knee jerks. The remainder of the tick was removed at this time with gradual recovery in five days.

In Other Countries: Case reports of tick paralysis from elsewhere than America and Australia are few. Sant' Anna's (41) patients, from Laurencó Marques, a port in Portuguese East Africa, almost certainly had some form of rickettsiosis; certainly they do not fit the clinical picture of tick paralysis as it occurs elsewhere. Garin and Bujadoux (42) reported a case from France. Their patient, a male of 48 complained of weakness and pain when raising his right arm. His spinal fluid gave a positive Wassermann test, and arsphenamine failed to produce noteworthy improvement in the weakness.

Veneroni's (43) two cases from Somalia are scarcely more convincing. The first was a boy of four who suddenly developed marked weakness of his legs an indefinite time after the attachment of a tick. When examined there was absence of all voluntary movement of the lower legs. Cutaneous reflexes were weak; tendon reflexes were absent. The child was sent home, but two weeks

later was perfectly well. Veneroni's second case was a female of six who showed tonic and clonic convulsions of the neck and face muscles, tachycardia, and tachypnea. The patient's mother had previously removed a tick from the child's neck. The patient was quite ill, but slowly improved and was asymptomatic within a fortnight. In both cases Veneroni surmised that the responsible tick was *Rhipicephalus simus*. No further details of these cases were given. It is possible that they represented forms of tick paralysis.

TICK PARALYSIS IN DOMESTIC ANIMALS

Failure of locomotion in domestic stock infested with ticks and prompt return to normal following the removal of the ticks has been described many times. It is not easy to be sure that these instances represent a disease analogous to tick paralysis in man for the reason that several diseases of domestic animals present clinical features which one might expect if a disease entirely similar to tick paralysis did occur in animals. Among these are distemper and Texas cattle fever. Complete pathological reports either from human or animal cases of tick paralysis are missing, and almost no attention has been given the blood picture. This last is important in ruling out various blood parasitic diseases such as piroplasmosis. Nevertheless, it is difficult to escape the impression that the disease in man has its counterpart in several animal species.

In Australia: The early observations of Hovell (1) and of Backhouse (2) have already been mentioned. In 1884 Bancroft (3) described paralysis of the hinder extremities of dogs and cats two or three days following the attachment of ticks. In his experience death occurred uncommonly in adult animals but young dogs rarely recovered. Anderson-Stewart (4) in a discussion of various animal poisons called attention to weakness in dogs infested with ticks. Some of these animals died from respiratory failure and some which recovered were left with peripheral nerve paralyses. It is possible that the subjects presenting this last feature had distemper. In 1921 Dodd (44) described tick paralysis in foals, calves, cats, and dogs, and also pointed out that the prognosis is better in younger animals. Ross (45) in 1932 reported vomiting and progressive weakness of the hind limbs of his own $5\frac{1}{2}$ month old cocker spaniel, which harbored numerous nymphs of *I. holocyclus*. These were removed and recovery was rapid, but shortly thereafter the dog was again covered with nymphs and again developed paralysis of his hind legs, with recovery again following removal of the parasites. He thought (63) that native fauna were immune to the disease, but this was not borne out by Smith (46), who reported that tick paralysis interfered with his experiments on "Q" fever, in which they used the bandicoot (*Peromyscus nasuta*), a small marsupial inhabiting the east coast of Australia. These bandicoots were obtained from near Brisbane, where *I. holocyclus* is rare. He observed paralysis in several bandicoots infested with large numbers of nymphs of *I. holocyclus*.

In South Africa: The most extensive outbreaks of tick paralysis have been described in sheep. In 1904 Malley (5) and in 1905 Borthwick (6) described the disease in South Africa. The apparently responsible tick was *Ixodes pilosus*,

but recently Philip (47) has noted that *Ixodes rubicaudus* also causes tick paralysis in sheep in Africa. Soon after the first frost in May the sheep would be found lying in the veld unable to move. If a herd was being observed at this time of the year, occasionally a sheep would be seen lagging behind the rest of the group. Soon it would walk with an unsteady gait, and eventually would lie down altogether. Within six hours paralysis of the extremities would be complete. The temperature was invariably normal. Most of the animals would recover in 48 hours unless a jackal killed them. Dipping promptly put an end to the disease in the herd. Borthwick autopsied a number of his sheep but found nothing.

In North America: In 1913 Hadwen (15) described an epidemic of tick paralysis in a sheep herd belonging to a farmer in Keremeos, British Columbia, who had imported 400 sheep the previous year from Montana. During March and April he lost 46 sheep and the following year many more developed the disease and 80 died. Hadwen, who was sent out to investigate this epidemic, found ticks on some of the sheep but saw no fresh cases. The tick was *Dermacentor andersoni*. Paralysis occurred regularly six to seven days after attachment. Hadwen felt that attachment of the tick along the spine was an important feature in the development of the disease, but subsequent observations have shown this not to be true. He mentioned an instance where the paralysis lasted for several months before recovery finally took place. In 1922 Bruce (48) recorded an epidemic in which 300 out of 400 sheep were affected in a district north of Kamloops, B.C.

Tick paralysis in cattle has been observed in British Columbia and Montana. Bruce (49) mentioned that "down with ticks" was the designation of the Montana veterinarians for a condition of unknown etiology which occurred in tick infested cattle, causing them to lie on the ground unable to rise, and which was cured rapidly by the removal of the ticks. Most of the cases occurred in the early spring (50). Moilliet (52) in 1937 reported an outbreak in cattle. There were 200 cases with 26 deaths in a herd of 638 animals. Five years previously in a nearby district 100 cases with 65 deaths were reported in a herd of 900. Most of those which recovered were well within a few hours after the ticks were removed from their necks, although some walked on their knuckles for a week or so.

There is scarcely any mention of the disease in horses, but Bruce (49) mentioned a rancher in British Columbia who had written that he had lost two horses, and thought that ticks, which almost covered the horses, were responsible. His animals had become so weak that they could not stand and "seemed stiffened up behind." Hutyra and Marek (53) mentioned the occurrence of the disease in rabbits.

While studying the life history and ecology of the moose (*Alces americana americana*) in the Superior National Forest in Minnesota and in areas northward in Ontario, Thomas and Cahn (54) learned from trappers that between February and May a moose occasionally becomes extremely active, running through the forest blindly and aimlessly, eventually to break down in the hind

or fore quarters and die. These animals were invariably covered and sometimes almost denuded by ticks. The common tick in this locale is *D. albipictus*. A moose with this disease was observed and a photograph published (67). They were able to collect 32 well authenticated cases. In view of subsequent experimental work with ticks obtained from these moose it seems doubtful that this is tick paralysis (vide infra).

In Crete: Tzortzakis and Papadakis (55) described an illness of sheep and goats in Crete characterized by high temperature, motor paralysis, leucocytosis, anisocytosis, and intraerythrocytic bodies. These animals carried ticks and the authors called the illness tick paralysis, but it seems more probable than an anaplasmosis or a piroplasmosis was responsible. The description of Blanc and Camienopetros (56) is more convincing. They included observations on cats, dogs, and sheep. Motor paralysis was the outstanding sign. *Ixodes ricinus* and *Haemaphysalis punctata* were the responsible ticks.

In Jugoslavia: In 1935 in several districts of Jugoslavia there was an epidemic of tick paralysis in cows and other ruminants. This was observed by Oswald (57, 58), who made the diagnosis. He obtained a variety of ixodid ticks from these animals, but found no one of them common to all the cases. The disease was known to the natives as "Shimteera," "Lejanitza," and several other terms, which seem to be only place-names. The animals when ill were awkward, staggered and fell, and exhibited diminished rumination and marked dyspnea. They died in three to four days unless the ticks were removed. The disease apparently had been known to the farmers of these districts for a number of years.

PATHOLOGY OF THE NATURALLY OCCURRING DISEASE

Satisfactory pathological studies on human or animal cases of tick paralysis are lacking. From the brief protocols available it is frequently difficult to determine whether histological study has been carried out. Ferguson (34) reported a 16-month old male who died with a flaccid paralysis and from whose scalp a tick, *I. holocyclus*, was removed an hour before death. This child had not been entirely well for about a month, a fact which throws some doubt on the diagnosis. At autopsy all portions of the brain showed intense engorgement and diffuse round-cell infiltration without perivascular cuffing. No mention was made of findings in other organs and no other pathological reports of the disease in man appear in the literature.

Borthwick (6) found no lesions in sheep dying of tick paralysis. Brumpt's (73) case of a dog bitten in the ear by two *I. holocyclus*, showed a normal brain and spinal cord. Tzortzakis and Papadakis (55) reported hyperemia of the central nervous system, but it seems likely that their sheep and goats died from an acute infectious disease.

EXPERIMENTAL TICK PARALYSIS

Investigations designed to demonstrate the cause and mechanism of tick paralysis have centered on the induction of the disease by attaching ticks to

laboratory animals, and by injecting organisms and extracts obtained from ticks. Efforts like those of Borthwick (6) and Dodd (44) to produce motor paralysis by using the blood of animals ill with tick paralysis, or like those of Hadwen (15) and Steinhaus (59) who used extracts of lung, liver, and brain, have been uniformly unsuccessful.

In a series of experiments reported in 1913 Hadwen (15) allowed eleven female and two male ticks to attach to a lamb. Eight days later the lamb was completely paralyzed. Two other lambs similarly treated developed motor paralysis six and eight days following attachment. In a later report Hadwen and Nuttall (16) described the onset of hind quarter paralysis in laboratory sheep experimentally infested with ticks eight days prior to the onset of symptoms. Ten days after tick attachment, incontinence and forelimb paralysis appeared; 16 days after attachment, symptoms had subsided. McCornack (26) allowed a tick removed from the axilla of a patient ill with a flaccid paralysis to attach to a guinea pig. Six days later the pig developed marked weakness and fever, and eventually died; Todd (11) was unsuccessful in producing paralysis in rats and lambs when using Berkefeld filtrates of triturated ticks. Sabbatini (14) on the other hand demonstrated collapse and flaccid paralysis in experimental animals following intravenous injections of unfiltered emulsified ticks.

Significant in the explanation of many investigators' failures are the experiments of Regendanz and Reichinow (60) who pointed out that paralytic symptoms follow only the use of gravid ticks with ripened eggs. Dodd (44) and Ross (61) were successful in producing paralysis in dogs by using adult female *I. holocyclus*. Despite the removal of the offending tick four out of five of Ross's dogs died from progressive paralysis. Ross conducted a very significant experiment on one of these dogs. He anesthetized the paralyzed animal and demonstrated a normal muscle response to faradic stimulation of the exposed peripheral nerve, indicating that the paralytic agent acted centrally.

Salivary secretions: It is apparent that some noxious agent elaborated within the tick and injected into the host must be responsible for tick paralysis. Ross in 1926 (61) in seeking an anatomical explanation of the usual 5 to 8 day incubation period of the disease, suggested the salivary gland as the source of such a noxious agent. This organ increases rapidly in size as engorgement proceeds (33); this increase is the result of hypertrophy of alveolar cells of the gland.

Nuttall and Strickland (14) cited Sabbatini's demonstration of an anticoagulant in *I. ricinus*, and demonstrated it in the salivary glands of *Argas persicus*. Cornwall and Patten (62) also found anticoagulant in the salivary secretions of *A. persicus* and showed that glands dissected five days after attachment of the tick contained only a feeble anticoagulant, whereas the glands obtained from ticks which had fed ten days were much more potent in anticoagulant and in agglutinating effect on red cells. Ross in 1926 (61) emulsified the salivary glands from several female ticks which had engorged for five days and injected the material subcutaneously into white mice. Their gait in an hour appeared stiff and difficult. Similar experiments on guinea pigs and dogs were negative; intravenous injections produced only a febrile response without

paralytic phenomena. Ross concluded from this work that "the causal factor in the production of the disease (tick paralysis) is a tick-derived toxin, this toxin being secreted by the salivary glands." Such a conclusion seems hardly justified by the experimental work cited. His results may well represent focal embolic phenomena induced by the erythrocytic agglutinating factors in the salivary emulsion. Recently Ross (63) has repeated his earlier experiments with the same results; Gregson (64) has been unable to confirm Ross's work.

Tick Ova: It has been routinely observed that ticks removed from patients or animals ill with tick paralysis are gravid females. With this in mind Regendanz and Reichenow (60), working in Germany with *Rhipicephalus sanguineus* and *Dermacentor reticulatus*, gave saline emulsions of tick ova subcutaneously and intraperitoneally to a number of laboratory animals, and with fair regularity produced paralysis of the extremities. The results of injecting this emulsion into dogs were not uniform. Several of the animals developed weakness of the hind limbs on the second day. Four out of the seven dogs injected died. One injected subcutaneously developed paresis of the legs three hours later. At least one had a pronounced spastic paralysis. Similar experiments were carried out with guinea pigs, rats, mice, rabbits, and canaries. In many, weakness of the extremities was apparent 24 hours after injection; many died. These authors found that the toxic agent was resistant to drying and 70% alcohol. It was inactivated at 85°C. in 15 minutes or 100°C. in one minute, but was resistant to 75°C. Eggs treated with KMnO_4 before being emulsified were still potent. Saline emulsions of the outer sticky coating of eggs failed to cause symptoms; the remaining eggs retained their toxicity. Regendanz and Reichenow believe that because of the rapid onset of symptoms following injection, a viral or bacterial etiology of tick paralysis seems unlikely. These workers feel that the responsible agent is a toxin originally formed in tick eggs, which later diffuses to some extent throughout the tick body.

More recently Steinhaus (59) was able to kill guinea pigs regularly with a Berkefeld filtrate of triturated *D. andersoni* eggs. Death occurred on the second day following the intraperitoneal injection. Cultures from the blood and organs of these animals were negative. Injections of emulsions of liver, spleen, lung, brain, and cord were innocuous. Surface sterilization of the eggs did not alter the results, but administering the eggs orally was ineffective. The active agent from the eggs was not dialyzable through a collodion membrane and was resistant to drying. Steinhaus believed that he was unable, on the evidence he could present, to identify the toxin from tick eggs with that responsible for tick paralysis.

Mlinac and Oswald (65) confirmed the above work with saline extracts of various Balkan tick eggs. Their extract when cultured on agar showed "non-pathogenic ubiquitous cocci and sporulating anthracoid bacilli." Its potency was destroyed at 85° C. in 15 minutes; pepsin did not destroy the 15 to 20% protein content or inactivate the active agent. Guinea pigs injected subcutaneously showed within several hours anorexia, depression, labored breathing, nasal discharge, and pronounced weakness of the extremities. The majority

of the animals died within 2 days. Blood from two animals taken shortly before death was injected into a normal guinea pig without effect. Eggs from *Hyalomma scupense*, *Boophilus calcitratus*, *Rhipicephalus bursa*, and *R. sanguinis* were equally effective. Gregson (66) found that a tick emulsion similar to that used by Oswald was lethal for 10 day chick embryos.

Recently the problem has been reconsidered by de Meillon (51) in South Africa. He injected emulsions of eggs obtained from *Rhipicephalus evertsi*, *Boophilus decoloratus*, and *Haemaphysalis leachi* into guinea pigs. There was a characteristic febrile response almost immediately, and in two or three days the animals showed anorexia, staring coat, disinclination to move, weight loss, diarrhea, hyperesthesia, and an occasional animal died. A dialysate of the emulsion gave the febrile response only. One of the guinea pigs developed a true motor paralysis 48 days after it was injected. On the basis of the evidence he has been able to present de Meillon does not believe that his or other toxic agents derived from tick ova are identical with the one responsible for tick paralysis.

Tick parasites: Hadwen and Nuttall (16) first suggested the possibility that the cause of tick paralysis, like Rocky Mountain spotted fever, relapsing fever, heart water fever and Texas cattle fever, may be a parasite existing within the tick and transmitted by tick bite. An interesting series of observations was made by Cahn and coworkers (54, 67, 69, 70). These investigators collected a number of ticks, *D. albipictus*, from a moose which had died in the manner described above (page 231). They allowed these ticks to attach to guinea pigs, rabbits, and a bull. In ten days many of the experimental animals, with the exception of the bull, showed a paralysis of the hind legs. Noteworthy, however, is the fact that in many of the protocols "walking movements of the legs" were noted shortly before death. This seems hardly consistent with a flaccid paralysis. Blood smears from these animals were generally negative, but in several febrile guinea pigs intra-erythrocytic blue bodies similar to those seen in piroplasmiasis were noted. Clumps of "red-staining material" were found in the blood plasma of animals which died from fever and paralysis. An encapsulated gram-negative rod, which they named *Klebsiella paralytica* was isolated from the gut of ticks obtained from dead moose. Injection of pure cultures as well as of culture filtrates of this organism resulted in paralysis, convulsions, and death in rabbits and guinea pigs within 24 hours. In contrast to the toxic agent from tick salivary glands and ova, mentioned previously, this toxic substance was found to be very labile.

Ross (61) was unable to produce any effect by injecting dogs with the intestinal contents of *I. holocyclus* which had caused fatal tick paralysis in his experimental animals.

In evaluating results obtained in experimental animals it is essential that one keep in mind the possibility that the observed effects may have arisen from extraneous and obscure sources. Many diseases of domestic and wild animals are characterized by failure of locomotion: Victims of Texas cattle fever are unable to stand, have muscle tremor and oscillatory movements of their hind

limbs. In *piroplasma canis* dogs refuse food, and walk, if at all, with a staggering gait (53); piroplasmosis of sheep is characterized by paresis of the hind quarters; serum jaundice of horses induced by injection of an anti-dysentery lamb serum leads to staggering gait and eventually complete paralysis (71). There is little doubt that many of the effects noted are the result of organisms transmitted to the animal by ticks, and not of a specific neurotoxin. Recently Russian spring-forest encephalitis has been shown to be tick-borne (72).

The hereditary transmission of the rickettsial organisms through generation after generation of ticks is well known; experiments using tick ova and extracts of tick ova are not adequately controlled to rule out this possibility. Injection of a substance which in vitro causes agglutination of erythrocytes might readily lead to embolization of the central nervous system and a prodigy of neurological signs. The sudden death of rabbits following intravenous injection of sterile filtrates of *Staphylococcus aureus* cultures is well known; it should not be surprising that similar filtrates from other organisms should be followed by rapid death when they are injected.

From the foregoing it seems apparent that various noxious substances exist in the salivary glands and in the eggs of ticks, but it is equally clear that with the information available it is impossible to identify any such agent with that responsible for tick paralysis as it occurs naturally. The failure of all experiments where blood or emulsions of viscera of animals ill with tick paralysis are employed seems to eliminate the possibility that an organism is responsible. The ease with which the rickettsioses can be transmitted bears this out. Before the pathogenesis of tick paralysis can be stated, the active agents from emulsions of tick eggs, from tick salivary glands, and perhaps even from the filtrates from organisms isolated from the gut of ticks must be isolated and treated as pharmacodynamic agents.

PATHOLOGY OF THE EXPERIMENTALLY PRODUCED DISEASE

Hadwen (15, 74) necropsied a lamb twelve days after three ticks had attached and six days after the appearance of motor paralysis. Congestion of the brain and a fibrinous exudate in the ventricles were found. Two other lambs which had become paralyzed six and eight days, respectively, after the attachment of ticks were necropsied and congestion of the meninges was found; the other organs appeared to be normal. McCornack (26) encountered no abnormal findings in a guinea pig which he necropsied six days after a tick had attached. He had obtained this tick from a patient ill with tick paralysis. At the time of death the guinea pig had weakness of its extremities. Dodd (44) in a similar experiment likewise found nothing except hemorrhage around the point of attachment of the tick, and a distended bladder. Ross (61) studied the pathological findings presented by a number of dogs on which *Ixodes holocyclus* had attached. Sections from various levels of the cord and medulla stained by Nissl's haematoxylin and eosin method showed marked congestion of the anterior and posterior horns. In some sections numerous capillary hemorrhages around the nerve cells and into the adventitial sheaths were noted. Perivas-

cular mononuclear cellular infiltration and distinct neurophagia were likewise present.

Thomas and Cahn (54) allowed *D. albipictus* to attach to guinea pigs. Autopsy of these animals four to ten days later showed an enlarged liver with small yellow nodules on its surface and a small bloodless spleen. Such changes are more representative of an acute infectious process.

The pathological effects obtained by injecting emulsions of tick eggs are more diverse and confusing. Nothing was seen grossly in animals killed with Regendanz and Reichenow's (60) tick egg emulsion, but several dogs showed Marchi degeneration of the cord on histological study. Routine histological sections taken from guinea pigs killed with de Meillon's (51) tick egg emulsion showed no significant abnormalities.

The diversity of findings is evidence in itself that much of the experimental work done in connection with this disease stands in no relationship to the naturally occurring disease. It is unlikely that permanent pathological changes are to be found because of the extremely rapid remission of clinical signs which occurs following the removal of the tick.

IMMUNITY

Because of the relative rarity of the disease and the uncertainty of much of the experimental work which has been done, little is known about immunity to tick paralysis. It seems clear, however, that relative immunity to the attachment of ticks can be achieved. In 1939 Trager (75), by allowing larvae of *D. andersoni*, *D. variabilis*, and other ticks to attach to laboratory animals was able to prevent subsequent attachment and engorgement of larvae and to prevent adult ticks from taking as much blood as usual. He used guinea pigs, rabbits, and deer mice. Extracts of larval ticks given intracutaneously to these partially immune animals produced an intense cellular reaction at the site of the tick's attachment. Non-immune animals showed no such reaction. Using an antigen made from cephalic glands, salivary glands, and the digestive tract of partially engorged adult female ticks he was able partially to immunize guinea pigs against the attachment of larvae of *D. variabilis*. With a larval tick antigen he was able to fix complement of serum from a guinea pig on which *D. variabilis* had attached.

Ross (61) in 1926 reported observations on two dogs. One of these died from paralysis five days after a tick was placed on it, nine days after recovery from a previous attack. The second dog developed slight incoordination, difficulty in rising, and an inclination to fall eight days after attachment of a tick and two months after recovery from a previously induced attack of tick paralysis. Further attempts to produce paralytic symptoms in this dog failed.

Dodd (44) felt that young animals were more often attacked, and that adults become gradually less susceptible with advancing age independently of prior infestation with ticks, but Bruce (49) found that the disease was uniformly distributed according to age in a herd of sheep which he studied. Human cases have been reported most frequently in children but do occur in adults.

Ross (63) discovered two dogs which seemed perfectly well despite the fact that forty to fifty ticks were engorging on them. These dogs were bled and a serum prepared. Five ml. doses of this serum seemed to prevent the development of motor paralysis in young dogs even though the ticks attached. The serum also was effective in the treatment of more than one hundred naturally occurring dog cases; it was apparently of value even after marked paralytic symptoms had developed. Details of these cases are not reported. Hamilton (33) mentions that an anti-tick serum is prepared by the Commonwealth Serum Laboratories in Australia, but notes that it must be given in ten to twenty ml. doses before the tick toxin has become fixed in the nervous system. This serum was not effective in preventing tick paralysis in bandicoots in Smith's hands (46). Neither is its effectiveness unequivocal from a study of Hamilton's case records.

Steinhaus (59) and Regendanz and Reichenow (60) were unable to demonstrate immunity to tick egg emulsions or extracts.

DISCUSSION

The large number of cases reported in man and the striking symptomatology and uniformity of the clinical picture of these cases leaves little doubt that such a disease exists. Although there are constant differences between American and Australian cases, in general they are similar. The paucity of information about blood or spinal fluid findings or the pathological changes involved in these cases accounts for there being no laboratory diagnostic method. Diagnosis must be made on the basis of circumstance and the clinical findings. Errors in diagnosis have been made frequently, but this is not to be unexpected. Neurological signs are regularly encountered in tick-borne Rocky Mountain spotted fever. Just why there should be differences between the American and Australian cases is not apparent. The striking difference is in the duration of the disease after the offending tick has been removed. In a few clinical reports symptoms persist to such a degree as to suggest that these cases might be bacterial or viral in nature.

There is also little doubt about the existence of a disease of domestic animals which resembles closely the pattern of the disease in man. Again, satisfactory means for objective diagnosis are lacking, and in many of the reported cases and epidemics it seems certain that an infectious disease was involved.

In contrast to the complexity of the etiology of tick paralysis is the simplicity of treatment. For the most part, either in man or in animals, this resolves itself into the removal of the tick. In human cases if bulbar signs are present more vigorous supportive measures, including the use of the Drinker respirator, may be resorted to. Hamilton's anti-tick dog serum has been given insufficient clinical trial to warrant critical opinion at the present time.

The cause of tick paralysis remains obscure. It is improbable that a specific bacterial, viral, or rickettsial agent is responsible, for transmission experiments using blood and macerated organs of ill animals have been uniformly unsuccessful, and, further, the remarkable subsidence of signs and symptoms following

removal of the tick seems incompatible with an established parasite within the host.

The features of the disease are most readily explained by hypothecating a toxic agent formed in the tick and injected into the host. This toxin might be formed within the tick ova and diffused into the salivary glands, it might be formed within the salivary glands, or it might be formed elsewhere and activated by the salivary glands. The origin and nature of this toxin remain undisclosed despite the large amount of experimental work which has been done. The most convincing experiments are those which demonstrate a toxic agent within the egg.

Eaton (40) noted the similarity of tick paralysis to coniine poisoning. He thought that the alkaline saliva might combine with tissue fatty acids, thereby displacing glycerin which could be acted on by any one of several saprophytic organisms with formation of butyric acid. Butyric acid in turn might combine with ammonia to form coniine. It is difficult to see how this necessarily complex synthesis could take place. Woltman in a discussion of Abbott's review (76) also noted the similarity of tick paralysis to coniine poisoning. Since in tick paralysis peripheral neuromuscular function is intact it would seem unlikely that coniines or similar alkaloids could be involved. These act on myoneural junctions as well as on synapses.

McKay (77) considered the mechanism of action of the toxin to be that of an antigen (sic) which increases the permeability of local blood vessels, with exudation of serum and pressure on the nerves. He thought the poison had a selective action also for the vagus center. There seems to be little to support this highly speculative point of view.

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THE CUTANEOUS ARTERIAL SPIDER: A SURVEY

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CONTENTS

	PAGE
Introduction.....	243
Description.....	244
Material and observations.....	251
1. The vascular spider in hepatic disease.....	252
Review.....	252
Observations.....	258
Case reports.....	262
2. The vascular spider in pregnancy.....	278
Review.....	278
Observations.....	280
3. The vascular spider in persons with vitamin-deficiency diseases.....	282
Review.....	282
Observations.....	283
4. The vascular spider in normal persons.....	286
Review.....	286
Observations.....	288
5. The vascular spider in miscellaneous conditions.....	289
Review and observations.....	289
Spiders and related vascular changes in the mucous membranes.....	290
Physiology.....	291
Gross and microscopic structure.....	295
Differentiation of the vascular spider from Osler's disease (hereditary hemorrhagic telangiectasia).....	305
Discussion.....	314
Resumé.....	321
Acknowledgments.....	324
Bibliography.....	324

INTRODUCTION

Outward and visible signs of internal disease have been fundamental to the art and science of medicine from ancient times. Nonetheless, students of internal medicine and dermatology have evinced only sporadic interest in the acquired impermanent arterial lesion in the skin variously termed *nevus araneus*, *nevus arachnoideus*, *nevus arachnoïdes*, *spider angioma*, *spider telangiectasis*, *spider nevus*, *spider cancer*, *tâche stellaire*, *étoile vasculaire*, and more simply, vascular or arterial "spider."² Some years ago this disorder of the small vessels

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² They are called "spiders" or "devils" by barflies who, apparently, have long been familiar with their connotation. The lesions will be referred to as spiders hereafter in this paper.

of the skin and its relationship to hepatic disease was brought to my attention by Dr. Louis Hamman and Dr. Warfield T. Longcope. Since that time, I have had opportunity to study the vascular spider in a variety of abnormal conditions as well as in apparently healthy persons. Instead of approaching the problem in relation to cirrhosis only, or hepatic disease, or pregnancy, or nutritional deficiency states, or in persons seemingly normal, I have pursued the study wherever spiders were encountered. This has given a panoramic rather than specialized point of view. One of the by-products of the investigation has been the realization that in some persons the spider is the specialized form of a general disorder of the blood vessels of the skin, sometimes accentuated locally as palmar and plantar erythema and often occurring in mucous membranes. Data have accumulated upon persons in the several categories of disease and apparent health in which the spider and associated vascular changes have been observed. It is the purpose of this paper to present the results of this investigation, a review of pertinent literature, and the features which sharply distinguish the vascular spider from the telangiectatic lesions of Osler's disease (hereditary hemorrhagic telangiectasia). Many observations and ideas which follow give testimony to the unfinished state of the investigation. Since active work on it has been suspended it was thought to be worth while to present the material and inferences derived, even though incomplete.

DESCRIPTION

The numberless variations in the size and shape of the cutaneous arterial spider make generalizations difficult. Nevertheless, certain oft repeated features permit the description of a generic norm. Such terms as *tâche*, *étoile*, and spider indicate the basic pattern so frequently seen. The typical example is characterized by three main features: body, legs, and surrounding erythema, plus various lesser attributes.

Body. First, the *central point* or *eminence* constitutes the body. This may be so small as to escape detection without magnification, or so large as to command instant notice. Ordinarily there is a direct relationship between the size of the center or punctum and the size of the entire spider. Exceptions occur. There is a tendency for the body of the larger ones to be elevated, sometimes as much as three to five millimeters, above the adjacent skin surface. When the central point is large and elevated, it may be seen to pulsate. Palpable pulsation is found more frequently. The larger the center, the more apt it is to be symmetrical, and nearly hemispherical in silhouette. In the sketches and pictures, a variety of forms are shown (Figs. 6-22).

Legs. Secondly, branching vessels, the *legs* or *radicles*, radiating from the central hub spread out parallel to the plane of the skin, just below the surface. These may occur as a few well-seen vessels of fairly large caliber or as a large number of clearly defined smaller ones; or the vessels may be hidden beneath the skin, the only indication of their existence being given by the erythematous area surrounding the central point. The vessels appear as branching or unbranching spokes becoming attenuated and fading towards the periphery. They may be lost to view as they dip down into deeper layers of the skin, and

reappear as an interrupted or beaded strand. Where many large vessels occur, they may be disposed in several parallel planes, spreading peripherally. They may appear to overlap in criss-cross pattern (Fig. 15). It is not uncommon to see macroscopic connections; and if oil is placed on the skin and magnification of twenty diameters is employed, small inter-connecting loops are seen very often. With this technique, branches of the sixth order may be counted in some lesions. In many instances, branches are not apparent to the unaided eye. The legs of the spider are irregular in direction and may twist, branch, coil, disappear for a millimeter or two, and emerge distally. These features are clear in the illustrations. When the spider occurs in a fold of skin, or in a place where there are wrinkles, there is a tendency for many legs to follow the lines in the skin. Isolated single vessels which become prominently displayed in the skin have enlarged presumably as a result of the same forces that give rise to the typical spider elsewhere. These vessels may appear as strands which resemble the scattered silk threads in American paper money; or they may unite to form a loosely or closely knit reticulum which in advanced stages becomes a telangiectatic mat. On close inspection, some of the isolated vessels exhibit one or more branches. When the fork is bulbous or beaded, the simplest form of spider occurs (see Fig. 22).

Erythema. Thirdly, the area of erythema surrounds the central punctum. It may be roughly circular, or may be star or cog-shaped. Usually it extends several millimeters beyond the clearly visible legs but in some cases the legs extend beyond the perimeter of the red spot. When the branches are not readily seen, the spider may appear as a circular area of erythema with a central red punctum or pulsating papule. Sometimes the central punctum may also be hard to find, and the lesion may simulate the early stage of an acne pustule (Osler). A pale ring may surround the blush area of the lesion, but this anemic halo is not very common.

Color. Distinctive of the lesion is its fiery red color, which results from the rich supply of arterial blood brought abundantly in very thin-walled vessels towards the surface of the skin. This color may be seen even when jaundice or pigmentation gives an abnormal hue to the background.

Temperature. The region encompassed by the vascular ramifications of the arterial spider is warmer than the adjacent skin (13). This may be explained by the fact that a large amount of rapidly moving blood is brought near the surface. The elevation in temperature above that of the neighboring uninvolved skin is roughly proportional to the size of the spider and may amount to as much as 2° - 3° C.

Direction of Blood Flow. Blood flows from the central body through the legs towards the periphery. This has been observed by many writers (13, 70, 99, 145, 147, 173, 174). It may be demonstrated by the application of pressure to the center, which causes fading of the whole area; or by enclosing the spider in a transparent capsule fixed to the skin, and gradually increasing the pressure (13). The erythema fades and recedes from the border towards the center, the whole being obliterated by adequate pressure. (See Physiology.)

Collecting Veins. In Figure 18 may be seen the arrangement of superficial

veins in the skin surrounding the territory occupied by the vascular spider. It appears that the return of blood from the capillary bed is effected by a system of collecting vessels about the periphery of the spider legs. Nothing like *venae comites* for the central arteries has been seen in our histological sections. It is well to emphasize here that the vascular spider is emphatically not an arteriovenous shunt in the sense of a glomus body, nor is it similar to the arteriovenous aneurysm which may follow injury to an adjoining artery and vein. Arterial blood is contained in the spider legs, however much they may resemble veins in their histological characteristics.

Pulsation. If the location is favorable or their size is large, spiders can be felt to pulsate. This is particularly noted when the lesion overlies bone, as over the forehead, sternum, or clavicle. Pulsation can be seen if a capsule is attached to the skin and the pressure within it is adjusted so that a stream of blood flows and ebbs to and from the central point into and out of the legs.

Variations in Appearance in Different Types of Skin. The superficial appearance of the spider is modified by the texture, elasticity, pigmentation, and thickness of the overlying skin, as well as by its nearness to the surface. This may be seen to best advantage in a person who has many lesions scattered over the body. When the skin is atrophic, much of the finer structure can be observed by the use of magnification. Examination of the lesion by means of a slit lamp permits visualization of the deeper structures in favorable cases. The erythematous macule, the large round pulsating boss, and other variations are included in the photographs and diagrams.

Absence of Hair. It is unusual for a spider to occur where hair is heavy. Rarely does it appear in the scalp, axilla or pubic regions. It may, however, occur on the face in the beard area, or on a hairy chest. Usually the territory which is erythematous has no obvious hair (See Fig. 18), although hair follicles are commonly seen in the microscopic sections.

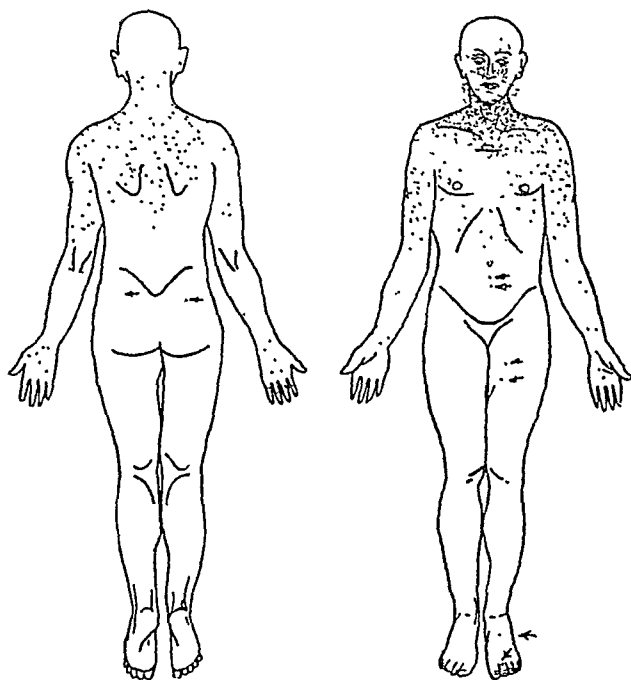
Distribution. The pattern of distribution is treated in detail under Physiology. Figures 1-5 portray the essential features.

Associated Changes in Cutaneous Vessels. An indication of the widespread alteration in cutaneous vessels associated with spiders is the paper-money skin. This type of change has been emphasized by Steinmann (173, 174) and by Patek, Post and Victor (147), who were struck by the ubiquity of vascular disturbances which rendered many vessels visible in regions of the skin where they are not seen normally.

In addition to the typical spider formation and the scattered strands of vessels in the skin, other characteristic phenomena are associated in many cases. Perhaps the most familiar is vascularization of the external aspect of the nose. Large vessels, firmly imbedded in or just beneath the skin, course over the nose from the nasomalar junction or emerge in front of the alae, imparting a livid appearance. Change in the degree of redness of the nose often proceeds *pari passu* with change in vascular spiders in other parts of the body.

Palmar and Plantar Erythema. Other alterations of cutaneous vessels include palmar and plantar erythema. A few of the salient points made in a recent

review (17) will be recalled. A number of patients with hepatic disease who have spiders have a conspicuous reddening of the palms and more rarely, of the soles. The thenar and hypothenar regions are peculiarly susceptible to this affection, and when it is extensive the finger pads and the bases of the nails

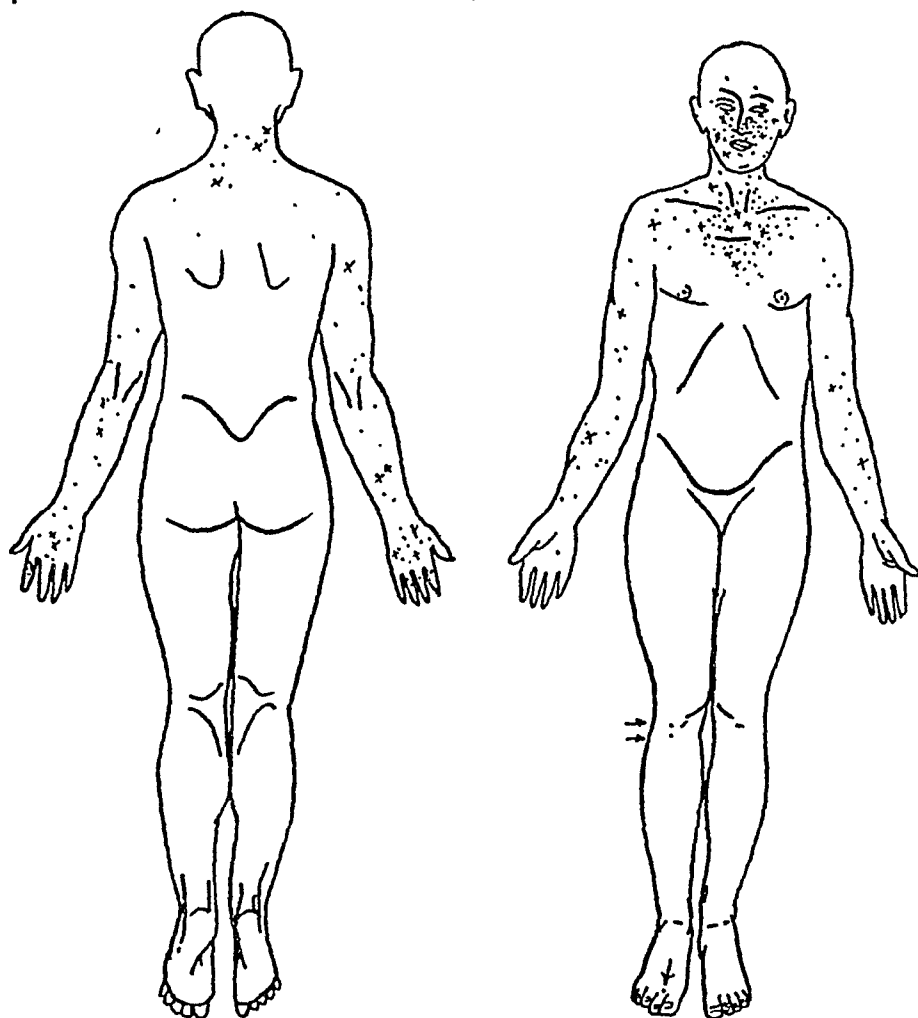


DISTRIBUTION OF SPIDERS
PERSONS WITH HEPATIC DISEASES

FIG 1. Diagram showing the location of the spiders in 41 subjects with hepatic disease, with a total of 793 lesions. Each dot represents the site of a single spider in one of the cases observed. Arrows call attention to the location of the umbilicus. Similar composite diagrams of the lower extremities of patients with hepatic disease show that

show similar changes. In extreme cases the whole palmar surface of hand and fingers shows the change. Characteristically the color is a combination of a bright redness with mottled spots of a cyanotic hue. A sharp boundary line separates the involved skin from the adjacent normal regions. There is an increase in cutaneous temperature and a strong capillary pulsation in the red parts. The distribution of this vascular change in the palmar pads, terminal

digits of the fingers, and the base of the nails, follows so exactly the distribution of glomus bodies as described and illustrated by Sucquet (177), that these structures appear to be the anatomical substrate for the erythematous changes in the hand.



DISTRIBUTION OF SPIDERS

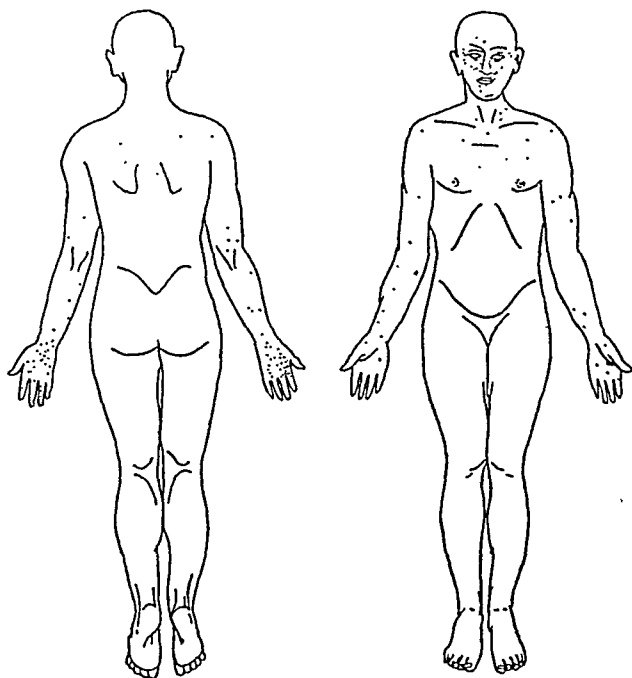
PREGNANCY: THE LESIONS MARKED WITH AN X PERSISTED, THE OTHERS DISAPPEARED AFTER GESTATION

FIG. 2. Diagram showing the location of spiders in 20 pregnant women (consecutive cases), with a total of 193 lesions. Each dot represents the site of a spider in one of the cases observed.

"Liver palms" have been noted by Perera (150) and by Ratnoff and Patek (153) in hepatic disease. Their occurrence in pregnant women, many of whom had vascular spiders, was first pointed out by Walsh and Becker (182). Lofgren (116) has also commented on them in pregnancy. He presented evidence that the cause might be estrogenic substances, or the general alteration in hormones associated with gestation. The same complication of pulmonary tuberculosis has been noted by Trosler (180) who believed it to be caused by toxins. The parallel clinical variations in intensity exhibited by vascular spiders and by

redness of the palms suggest a common cause, at least for lesions associated with hepatic disease, pulmonary disease, and pregnancy.

The combination of *clubbing of the fingers* and digital erythema has been noted in cirrhosis (17). Since the digital erythema includes an increase in blood flow made manifest by increased skin temperature and capillary pulsa-



DISTRIBUTION OF SPIDERS

PERSONS WITH B-COMPLEX DEFICIENCY DISORDER (FIRST DECADE)

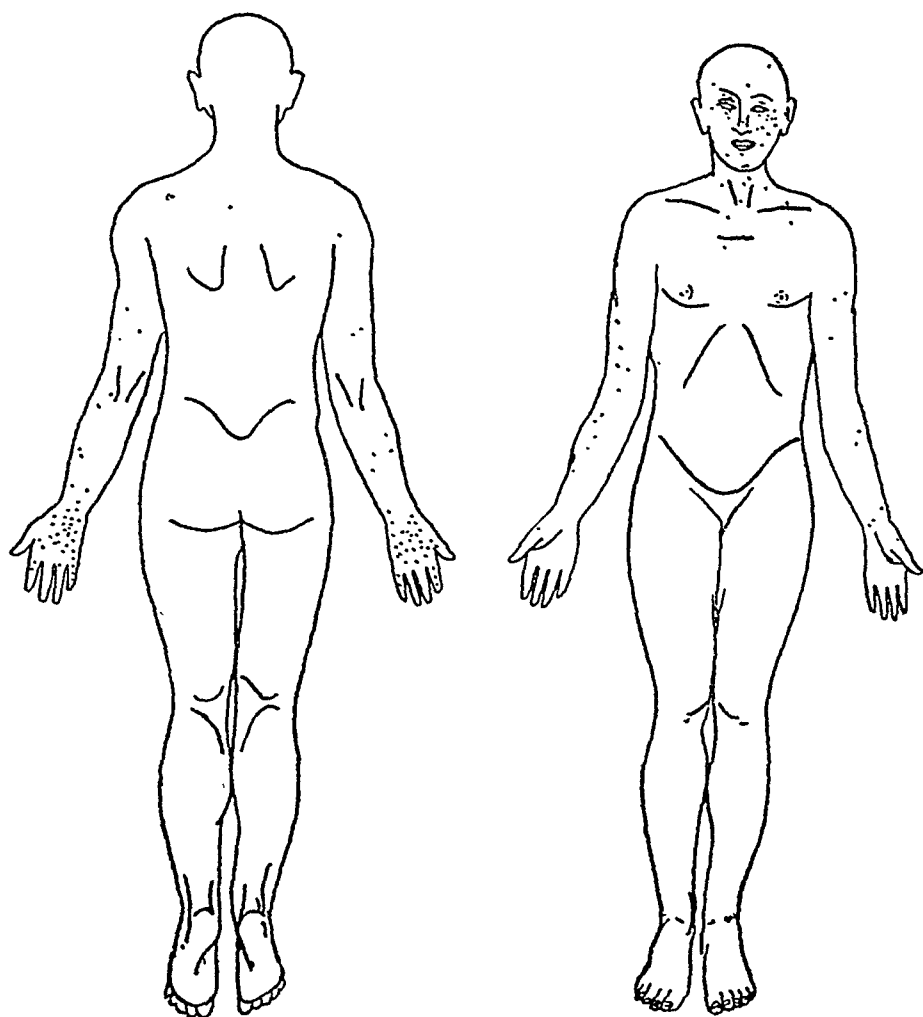
FIG. 3. Diagram showing the location of spiders in 49 subjects with a total of 164 lesions. Each dot represents the site of a spider in one of the cases observed.

tion as well as by redness, the criteria of Mendlowitz (129) for clubbing are fulfilled. It may be strongly suspected that the clubbing of fingers found in hepatic disease results from the same forces which give rise to vascular spiders and palmar erythema. Reasons for the irregular occurrence of clubbing, spiders and red palms remain obscure.

Post Mortem Fading. Unless the site of a spider is marked, the lesion may be impossible to find after death. Fading is invariable, although some of the

larger spiders may remain for 24 hours or longer as faint ghosts. This indicates a degree of contraction even in the thin-walled radicles. A similar but abrupt fading is seen when a spider is removed during life (13).

Vascularization of Mucous Surfaces. Similar vascular changes in the mucous membranes of the body may occur in association with cutaneous spiders. This



DISTRIBUTION OF SPIDERS

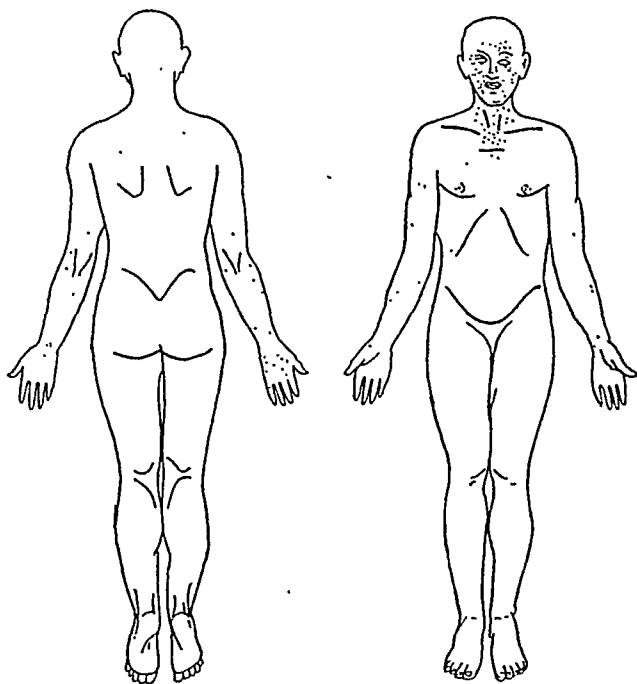
PERSONS WITH B-COMPLEX DEFICIENCY DISORDER (SECOND DECADE)

FIG. 4. Diagram showing the location of spiders in 27 subjects with a total of 134 spiders. Each dot represents the site of a spider in one of the cases observed.

fact has been emphasized by French clinicians, who attribute much of the bleeding in chronic hepatic disease to these lesions. The mucosal telangiectasis often does not follow the spider-pattern so prominent in the skin, but may occur in any form from a short strand to a complex mat.

A final word should be added about various types of pigmentation occurring in persons with vascular spiders (See Fig. 19). Pigment spots may be dark or

light, punctate, splotchy or irregular. I do not know the source, nature, or significance of such pigmentation, or whether it is related to the pigmentary changes in pregnancy.



DISTRIBUTION OF SPIDERS

PERSONS WITH B-COMPLEX DEFICIENCY (AGED 20 YEARS AND OLDER)

FIG. 5. Diagram showing the location of spiders in 51 subjects with a total of 125 spiders. Each dot represents the site of a spider in one of the cases observed.

MATERIAL AND OBSERVATIONS

Observations have been made upon 430 persons having cutaneous vascular spiders: One hundred twenty were malnourished persons with no clinical hepatic disease, seen in the Hillman Hospital in Birmingham, Alabama, during the spring and summers of 1940-41-42; 107 were normal persons without indication of hepatic disease, past or present; pregnancy, or deficiency disease; 106 were persons with hepatic disease; 56 were inductees seen in a group of 1000 young men aged 21 to 28 years, examined at Fort Thomas, Kentucky, prior to induc-

tion into the Armed Forces in 1941; and 41 were women who acquired spiders during pregnancy. Of the total number, 267 cases were studied in detail and some have been followed at intervals for six years. The records, figures, diagrams, and case histories are from this smaller group. For the most part, the rest of the persons listed above were seen once or only a few times. Some of the normal persons who had vascular spiders have been observed for three or four years, but records on the normal group are less complete than the others.

When this investigation was undertaken, it was hoped that clinical study might reveal some etiological factor which would account for the appearance of spiders during the course of various diseases of the liver. It was an unlooked-for event when similar vascular lesions were found under other circumstances. Nevertheless, the data collected in the early phase of the study served to demonstrate the lack of exact correlation between any single clinical or laboratory finding in hepatic disease and the occurrence of the spider. Nor was there any exact relationship between the severity of a particular case of hepatic disease and their occurrence, although chronicity and severity made their advent more likely.

Charts showing the size and location of spiders have been kept, and the changes recorded in each case. Many lesions were photographed. Tracings or free-hand sketches of a number of spiders were kept so that the natural history of a single lesion could be scrutinized. Experiments were carried out to discover methods of measuring indirectly the intravascular pressure of different parts of the spider. Transparent capsules held in place with collodion or rubber cement were connected with a mercury manometer, and the events following slow changes in pressure were observed. Additional studies included comparison of black-and-white and infra-red photographs; biopsy and serial sections of many lesions; use of vitamin B-complex in treating persons with spiders, and the use of estrogens in an attempt to evoke spiders in susceptible persons.

THE VASCULAR SPIDER IN HEPATIC DISEASE

Historical Review

It is impossible to decide whether or not certain vague descriptions found in ancient medical writings concern the vascular spider. There is no clear description of them in the works ascribed to Galen or Hippocrates. The later does not include them in his classical description of that aspect of hepatic disease to which posterity has given the name Hippocratic facies. In some of his case histories he referred to lesions resembling flea bites, which appeared in crops, but there is no hint to help us distinguish them from purpura, scurvy, vitamin-K disorders, or typhus. Various angiomas are referred to casually in medical writings of the Middle Ages but the interest was often centered on a suspected relationship to witches rather than to disease. Nothing can be made out of the large body of literature on the nevus maternus or mothers' marks, which has been of interest chiefly to the gullible as grounds for their fanciful belief in maternal gestational influences on the offspring. I can find no reference to

vascular spiders in the writings of Morgagni, Laennec or Bright, who understood many of the clinical relationships of diseases of the liver. No description occurs in the works of Addison, Frerichs or Fagge upon hepatic disorders. It has not been possible to make a comprehensive search of the very old German and French dermatological and medical writings, but if any knowledge existed about the vascular spider it has not been handed down to modern writers. Therefore we may conclude that only in relatively recent times have these blemishes in the skin effectually aroused the curiosity of the physician. Perhaps this is not strange when we recall that the striking entity of hemorrhagic telangiectasia was not generally recognized and was certainly not defined until Osler's paper brought out its interesting natural history (135, 137).

The first specific reference to an indubitable instance of the vascular spider was made in 1869 by Erasmus Wilson (189), an English physician specializing in dermatology. His brief note is given here in full.

"A publican, aged 30 years, had for some time yielded to the temptation of his calling, and had thereby injured his health, when he was suddenly attacked with epistaxis and to the epistaxis succeeded copious bleeding from the gums. After some time, and subsequently there appeared on the face, the neck, the hands, and the arms, an eruption of red papulae with a diffuse areola. On presenting himself for consultation there were six of these papular spots on the face, chiefly on one cheek, two on the neck and three or four on the hands and forearms. It was evident, on careful examination, they were angiomas; the central prominence was vascular, and around this was a plexus of venules spreading out to the breadth of a quarter or half an inch. In one or two of the spots the central prominence was absent and a plexus alone existed, resulting from angiectasia, or multiplication and hypertrophy of the venous capillaries of the skin. The case is very rare, a sudden eruption of angiomas, and its association with hemorrhage from the mucous membrane of the nose and mouth is very instructive. We are unaware of the conditions of the economy which may tend to the sudden hypertrophy of blood vessels, but we can easily understand how such an occurrence, taking place upon the mucous membrane, might lead to serious hemorrhage; and there is no reason to suppose that the cause of the epistaxis in the instance before us, and the bleeding of the gums may not have been a sudden hypertrophy of blood vessels such as we have just described as appearing on the skin. And it appears to us that as a result, to the well-known hemorrhagic diathesis as a cause of hemorrhage there must also be added a sudden hypertrophy of blood-vessels and rupture of their coat as exemplified in the case before us."

This excellent picture has remained buried. The lesion was characteristic and very well described. Association with over-indulgence in alcohol and presumably with cirrhosis is of great interest. The hemorrhages probably arose from the nasal mucosa. These observations led to no investigation to ascertain the validity of the speculations aroused in the mind of their author.

The second reference to vascular spiders in hepatic disease, and the first study devoted to the problem, came from the French clinicians, Hanot and

Gilbert (91) in 1890. They described the *étoile vasculaire* and must have realized the arterial nature of the vessels, referring to them as "*tâches érectiles véritables*." In addition they observed that these *étoiles* were not necessarily permanent, having disappeared in one patient with cirrhosis who was much improved when he was seen again four years after his initial examination. They showed that cutaneous vascular spiders have some relation to cirrhosis, are arterial in nature, and may disappear with amelioration of the hepatic disorder. Their findings have not been known to many subsequent writers on the subject.

In his classical study of hemorrhagic telangiectasia in 1901, Osler (135) made some interesting remarks about spider angiomas. He believed that the dilated vessels forming the radicle were veins converging upon the "central bright red nodule projecting a little beyond the skin." He commented on the superficial resemblance to the cutaneous lesion of acne. In his own words—"Angiomas have a curious relationship with affections of the liver. In cirrhosis, in cancer, in chronic jaundice from gallstones spider angiomas may appear on the face and other parts. They may be of the ordinary stellate variety like the stars of Verheyen on the surface of the kidney, or the entire area of the star may become diffusely vascularized, so that there is a circular or ovoid territory of skin looking pink or purple, owing to the small dilated veins. A dozen or more may appear on the trunk or even large ones may disappear. And lastly, in a few cases of disease of the liver I have seen large mat-like telangiectases or angioma involving an inch or two of skin, and looking like a very light birth-mark, but which had appeared during the illness. The skin was not uniformly occupied with the blood vessels but they were abundant enough in the deeper layers apparently to give a deep change in color and to form very striking objects. The dilated venules on the nose, and the chaplet of dilated veins along the attachment of the diaphragm are not infrequently accompaniments of the spider angiomas in cases of diseases of the liver. I have recently seen the spider angiomas appear in the face in a case of catarrhal jaundice." Later students have added little to these early descriptions, although the belief that the vessels were venules has been discarded.

Bouchard (32) made a significant contribution to the subject in 1902. He stressed the fact that the affected vessels were on the arterial side of the capillaries. He was apparently the first to see spiders erupt, fade away, and return during the varying clinical course of cirrhosis and he put great emphasis upon their direct relationship to the severity of the disease. It was his opinion that they appeared in areas in the skin which had been subjected to some trauma. He described similar lesions in the mucosa of the mouth and pharynx. Perhaps some of his patients with bleeding lesions were suffering from hemorrhagic telangiectasia (Osler's disease), although hemorrhage from mucosal spiders has been described by others (78, 91, 173, 174).

In 1903 Gilbert and Hirscher (78) reported the occurrence of vascular spiders in 107 persons with hepatic and biliary disease, including Laennec's (alcoholic) cirrhosis, tuberculosis of the liver, Hanot's (biliary) cirrhosis, familial jaundice, and other forms of hepatic disease. They thought that the characteristic

vascular spider should always excite the suspicion of liver disease, even though the disease be latent clinically. Upon grounds not exactly clear they concluded that on the hands and face, spiders were arterial in nature, while on the trunk they were composed of capillaries. Pulsation was specifically noted. It had previously been implied by Hanot and Gilbert (91).

In 1904 Parkes Weber (139), who has contributed a series of distinguished reports on vascular spiders and related telangiectatic states (139-146), expressed his belief that they were "induced by a small inflammatory papule of the skin." Subsequent observers have expressed a similar opinion.

The vascular spider was noted by Sir James Galloway (75) in 1908. He stressed its evanescent character, its appearing and fading with relapses and remissions in cirrhosis. Somewhat later (76) he described and pictured an advanced stage of this vascular phenomenon occurring in a soldier with syphilis, tuberculosis, a large liver and anal fistula. He called attention to the palpable pulsation in the larger lesions and to the bleeding that occurs with mild trauma.

Castaigne and Chiray (40), in the 1910 edition of their text, remarked that patients with Laennec's cirrhosis "have arterial varicosities and it is not uncommon to encounter one or more arterial nevi of recent date." They did not, however, remark on the spider form, although the concept of arterial varicosities suggests that they were well acquainted with it.

Frick (73), in 1912, reported an atypical example in a man suffering from carcinoma of the liver. It is possible that a disorder of a different kind was present since the lesions remained clearly discernible after death.

In 1914 Sibley (166) described the case of a woman who had vascular spiders showing a more or less symmetrical distribution. It is not clear that she had hepatic disease. In any event the vascular spiders faded while the patient was still under observation.

The nature of Adamson's (2) case (1918) is by no means clear but it may have been of the same variety.

In the volume of Contributions to Medical and Biological Research dedicated to Sir William Osler (1919) there is a report by Gwyn of a patient with Weil's disease in whom vascular spiders developed (89). I have seen no other example referred to and this lesion is not mentioned in the review of Weil's disease by Ashe, Pratt-Thomas and Kumpe (8).

A general consideration of angiomas by Emile-Weil in 1927 gave a good account of the occurrence of the spider-like lesion in cirrhosis (62). He implied but did not describe differences between the acquired vascular spider and other angiomas.

In 1928 Roles (160) reported a case of multiple telangiectasia with splenomegaly. From the description it seems probable that this represented the acquired vascular spider of cirrhosis rather than an unusual complication of Osler's disease, although others have interpreted it differently (69).

Rolleston has written of the clusters of dilated vessels or stigmata on the face (161). He said that when cirrhosis is advancing, small angiomas may crop up all over the surface of the body, and in exceptional instances may unite to

form areas of considerable extent. Elsewhere (162) he remarked that "small angiomas, probably due to toxemia and sometimes appearing in crops when the disease is advancing, are common in the skin generally, and when on mucous surfaces may account for epistaxis and for false hemoptysis and hematemesis."

In contemporary French medical literature there are many articles on the vascular spider. Laffitte (111) believed that it was similar in nature to other arterial nevi of the skin. Steinmann (173, 174) wrote two excellent reviews on the subject and was the first to discuss the morphology of the vascular lesion in detail. He called attention to the irregularities of the legs of the spider which dipped down in places so as not to be visible at the surface, giving the impression of an elongated spiral. He stated that pressure applied to the center caused the peripheral portion of the lesion to disappear. Arterial pulsation was readily detected in some spiders, especially the larger ones with elevated centers. Steinmann was one of the first to stress their curious distribution; their rarity or absence from the legs and lower part of the body; their frequency in the exposed areas of the face, cheeks, nose, brows, forehead, forearms, palms, fingers and upper aspect of the chest. He emphasized the fact that they showed a close relationship to the functional state of the liver, fading with remissions and developing or recurring with exacerbations in the severity of the disease. This was correlated in his patients with changes in the rose bengal test of liver function. He saw spiders appearing two or three years before ascites first occurred, at a time when the only indication of hepatic disease was digestive disturbance, sometimes with slight icterus. Hemorrhage from mild trauma to a lesion, especially on the mucous membranes, often called attention to its presence. Finally he noted that after death no traces of the lesion could be found unless it was very large and was angiomatous in character. Fiessinger (67) arrived at similar conclusions. He believed that the arterial spider was of prognostic significance since he observed instances of its fading in patients who recovered, but it is not clear that he was able to predict future improvement in cirrhosis on this basis. He was the first to call attention to similar vascular changes throughout the skin without typical star formation. Loeper, Loew-Lion and Netter (115) stressed the sudden explosiveness of the eruption and the prognostic as well as diagnostic value of the *tâches stellaires*. They were impressed by the association of these lesions with the ascitic and splenomegalic phase of cirrhosis, rather than with any particular type of cirrhosis. They emphasized the occurrence of submucosal lesions in the nose, mouth and pharynx and their rôle in hemorrhage. In some autopsy specimens the liver had extensively dilated portal spaces which were thought to be similar in nature to the vascular change in the skin. Finally, these authors observed that a high level of tyramine in the blood and ascitic fluid seemed to parallel the advent or enlargement of the cutaneous *tâches*.

Eppinger (65) summarized his rich experience with the cutaneous spider in his comprehensive monograph on hepatic disease published in 1937. He had been struck by the distribution of these lesions, never having observed them in regions not drained by the superior vena cava.

Eller (60) in 1937 reported an example in a 45-year-old white woman addicted to alcohol. The lesions developed first on the knees, later on the face. The discussion following his article gives a good example of the prevailing confusion about the nature and significance of angiomas in general and acquired vascular spiders in particular.

Bloomfield (30) in 1938 observed vascular spiders in 39% of eighteen patients with chronic hepatitis who were studied for long periods of time. In one instance most of the spiders had faded after a two-year interval during which the manifestations of cirrhosis subsided. There was no single factor in the reported clinical or laboratory findings which was directly correlated with this change.

In 1938 Williams and Snell (188) published an excellent description of six cases of pulsating angiomas in hepatic disease. They suggested that the spiders of hepatic disease were related to the glomus body and indeed their sections of a large pulsating lesion revealed the same tissue in the arterial wall as is found in the typical arteriovenous connection so elaborately described and reconstructed by Masson (126, 127) and by Popoff (152). In their discussion, Williams and Snell described the well known and clearly dissimilar vascular changes in the cutaneous vessels and overlying skin in Osler's disease, although elsewhere they assumed the identity of the two types of lesions.

Comment on spider nevi is included in Watson's article on regurgitation jaundice (184). He emphasized the distribution in the upper portions of the body, connecting this phenomenon, as did Eppinger, with the drainage area of the superior vena cava.³ He had never observed typical multiple nevi except in the presence of hepatic disease.

The most extensive study of the vascular spider associated with cirrhosis of the liver, one which combines an excellent physiological analysis with histological sections and descriptions, was reported by Patek, Post and Victor (147). These authors have added greatly to knowledge of this abnormal vascular structure and in their paper is the clear statement that "the acquired type of spider does not conform to descriptions of the congenital lesions" (i.e., Osler's disease). They found that 76% of 63 patients with cirrhosis of the liver exhibited spiders. They reviewed some of the previous reports and demonstrated beyond cavil that spiders fade on pressure, pulsate, are arterial in nature, and have an intra-arterial pressure around 85 mm. of Hg. which is somewhat lower than pressure in the brachial artery, but distinctly higher than capillary pressure in the fingers. The direction of blood flow is centrifugal, from the body through the radicles to the periphery. Their pharmacological investigation revealed that the smaller branches of the spider reacted to adrenalin and histamine in the same manner as the minute skin vessels. As might be expected from the arterial structure, lesions fade and may disappear after death, although the larger ones may leave a tell-tale region of increased lividity. These authors emphasized the point that the skin elsewhere was apt to exhibit dilated vessels not arranged in the typical spider pattern. They did not, however, mention any similar changes

³ I have recently been informed by Dr. Watson that he has subsequently encountered spiders on the lower aspects of the body (185).

in the mucous membrane. Their histological studies indicated a distinction between two types of spiders. One was an enlarged and dilated artery with branches from the stem going on to merge with the capillaries. The other variety was composed of a central stem artery which resembled the arterial side of an arteriovenous glomus shunt but had this significant difference, that it broke up into radiating branches which continued to the capillary bed at the periphery and did not empty directly into veins. The branches were thinly covered vessels which in structure more closely resembled veins than arteries, but contained arterial blood. This may account for the difference in opinion about the structure of the vascular spider. This difference may have resulted from studying one of the several parts rather than the whole, or perhaps only one of the two types.

Another detailed study of these lesions, one of the few that are illustrated with photographs, was published by Čičováčki (47). He found the lesions in 56% of 46 patients with cirrhosis. He noted their distribution, their variation with the changing stages of cirrhosis, and their occurrence in non-alcoholic cirrhosis. Curiously enough he believed that spiders were pathognomonic of cirrhosis and permitted the exclusion of other hepatic disorders. He brought out evidence for associated endocrine disorders, hairlessness, changes in the hypophysis, and atrophy of the testes, phenomena which have been described as occurring in the cirrhosis of hemachromatosis (5, 6, 112). In discussing the nature of these phenomena he called attention to *Chvostek's habitus* in cirrhosis (43, 44) and speculated upon a common constitutional cause for cirrhosis and vascular spiders.

A similar suggestion has been advanced by Parkes Weber in several of his notes on vascular spiders (139-146), although he is inclined to attribute the eruptive phenomenon, the provoking force, to an inflammatory reaction. If read aright, he considers the spider to be a mycotic aneurysm of the terminal cutaneous artery of Renaut (154), which may disappear when the infecting organism dies.

Ratnoff and Patek (153), in their recent monograph on Laennec's cirrhosis, reported that spiders had been described in only 15% of 386 cases and "liver palms" in slightly more than 4%. The data were incomplete, which probably accounts for the lowness of these figures as compared with those in the earlier study by Patek, Post and Victor (147). This underscores the necessity of judging the incidence of such lesions from a study centered upon them rather than from one that deals with the underlying disease.

Observations

It became apparent early in this investigation that there was no commonly used test of hepatic function nor any clinical sign of liver disease which was invariably associated with the presence of the vascular spider in a particular patient, at a given instant. This held true for a large series of function tests and for all the diagnostic signs of cirrhosis. There were correlations, however, which showed significant trends. When a comparison was made between a

group of persons with hepatic disease and spiders, and a similar group with no spiders, two facts emerged. Spiders were more frequent when the hepatic disease was severe than when mild; and they occurred more often in chronic than in brief diseases (Tables 1 and 2). There were enough exceptions to invalidate such a rule in individual cases.

A clinical and laboratory study of particular cases over a long period of time indicated that no sign or symptom heralded the coming of vascular spiders; and when they were established, no change in function or sign anticipated their disappearance. When jaundice was deepening, or ascites accumulating,

TABLE 1
The occurrence of vascular spiders in persons with hepatic disease

TYPE	WHITE MALES		WHITE FEMALES		NEGRO MALES		TOTALS	
	with spiders	without spiders	with spiders	without spiders	with spiders	without spiders	with spiders	without spiders
Laennec's cirrhosis	61	19	12	3	1	5	74	27
Cirrhosis and hepatoma	3	1	1				4	1
Cardiac cirrhosis	4	7		5		2	4	14
"Fatty liver"	1	1		1			1	2
Hemochromatosis	1	2					1	2
Hepatitis ("Catarrhal jaundice")	5	5	3	7		2	8	14
Post-arsphenamine hepatitis.	1	1			1	1	2	2
Post-bismuth hepatitis			1				1	
Weil's disease	1	3				4	1	7
Gumma of liver			1		1		2	
Chronic alcoholism and lobar pneumonia	2	18		5		11	2	34
Common-duct stone with jaundice	2	4		5		4	2	13
Carcinoma of head of the pancreas		3		1		2		6
Carcinoma of rectum with hepatic metastasis		3	1	3			1	6
Felty's syndrome	1						1	
Total	82	67	19	30	3	31	104	128

No spiders were encountered in female negroes

new spiders were apt to appear, or old ones to return, or existing ones to enlarge, but exceptions occurred often enough to exclude these events as measures of the specific agency which was also responsible for the changes in the vessels of the skin. Likewise the clinical improvement often presaged the disappearance of a spider, but occasionally it did not. Moreover, in a particular patient one vascular spider might appear or enlarge while another simultaneously faded or disappeared. This suggested the probability of a dual causation, some local force working on the skin vessels affected, as well as an underlying humoral cause associated with disease of the liver.

In Table 1 are listed all patients with hepatic disease examined for vascular spiders. The numbers do not indicate the relative incidence of the several

diseases, since only cases personally observed are included. The proportion of cases with vascular spiders is much higher than would be found in a study primarily based on hepatic disease (153). Because of the coöperation and interest of the house staff, examples were found before the nature of the underlying disease was established, thus weighting the figures on the positive side. In some cases spiders were not found until a later hospital admission, or until repeated tours of inspection had been made. Since the groups in Table 2 are not of uniform size but merely represent consecutive cases seen at random, a too close analysis of the percentages is not justified. The data suggest that men with hepatic disease are more likely to acquire spiders than women. Among Negroes, whose addiction to alcohol is high in the class of patients studied,

TABLE 2

Comparison of data in persons with Laennec's cirrhosis with and without vascular spiders

	WITH SPIDERS (74 CASES)	WITHOUT SPIDERS (27)
Average age.....	46	54
Sex		
Males.....	62	24
Females.....	12	3
Race		
White.....	73	22
Negro.....	1	5
Icterus index (average).....	36	10
Bromsulphalein retention at 30 minutes (average)...	42%	36%
Positive Takata-Ara reaction.....	83%	93%
Serum albumen (average).....	2.9	2.6
Serum globulin (average).....	3.5	4
Palpable liver.....	90%	67%
Palpable spleen.....	39%	52%
Collateral veins over abdomen.....	56%	26%
Ascites.....	69%	67%
Edema.....	60%	74%

cirrhosis was uncommon, and spiders rare. It is of interest that they occurred at all. They were seen only when the skin was fairly light (see Case 2). There were two possible examples in very dark-skinned subjects but the suspected lesions could not be obtained for histological verification so these cases were excluded. When the averages in Table 2 were computed it was found that the extremes of high and low values were about the same in the two groups. It was easy to find cases in which severe jaundice, ascites, and chemical evidence of hepatic failure had existed for some time but no vascular spiders had appeared. Several persons who had died from liver disease never had spiders. Nonetheless the spider usually indicated severity and chronicity in hepatic disorders.

In the data on patients with cirrhosis in Table 2, the average age of those with spiders was eight years less than that of those with none. This was true of the distribution as well as of the averages. The meaning is obscure. Figures for

sex and color may be considered as percentages since data on 101 cases are given in Table 2. A slightly higher percentage of women (80%) than men (72%) had spiders but there were relatively few women in the series. The icterus index and bromsulphalein retention indicate a more severe stage of cirrhosis in those with spiders, although the Takata-Ara and serum protein values indicate a trend in the opposite direction, as does the less frequent occurrence of ascites. An enlarged liver was found more often in those with spiders than in those who had none. The rather sharp difference in the percentages of cases with and without collateral veins has aroused the suspicion that the forces giving rise to vascular spiders may also favor the hypertrophy of collateral vessels when obstruction exists, although there is no direct evidence bearing on this point. The spleen was enlarged relatively more often in the absence of spiders than when they were present. All in all, these data should not be emphasized too much, for the numbers are small; and one should look for the cause of spiders in the circumstances prevailing while they are appearing or increasing rather than after they are established.

Of the first 25 patients with cirrhosis and spiders followed for four years, all but eight are known to be dead (two could not be traced). Only three of 23 cirrhotic patients with no spiders are dead after the same length of time. This is in keeping with the observation that spiders occur in severe hepatic disease.

These observations on Laennec's cirrhosis were extended by studying patients with other kinds of jaundice and with other indications of hepatic failure. Although the spider has been found most often in cirrhosis, and most articles about its relation to disease of the liver are based on this type of hepatic disease (32, 40, 47, 78, 91, 113, 147, 156, 162), its occurrence in a wide variety of affections of the liver becomes obvious from inspection of Table 1. In addition to the cases of Laennec's cirrhosis in which spiders were found, they were discovered also in patients with cardiac cirrhosis, fatty liver, and hemochromatosis. Their presence in such a high proportion of the cases of hepatitis ("catarrhal jaundice") was surprising.⁴ The lesions were less numerous and smaller than in the more protracted hepatic diseases so that many would have been overlooked without careful and repeated search. Among the few patients suffering from toxic hepatitis there were several with spiders. One patient whose illness was diagnosed as Weil's disease (unverified) had spiders. In this series of cases spiders were not found in persons affected with carcinoma of the head of the pancreas with chronic jaundice. This formed an exception to the rule that prolonged hepatic disease favors the eruption of spiders. The other hepatic diseases associated with spiders are represented by such scanty material that the significance is not clear. No further evidence is needed to demonstrate the non-specificity of the kind of hepatic lesion which may serve as a background for the spider. Thus it was concluded that neither a special type of hepatic disease, nor the severity nor chronicity of this disease was invariably responsible for

⁴ No spiders were seen to develop during the acute phase in some dozens of cases of hepatitis I observed in soldiers in 1942, although Turner has seen them in this condition; not more often, however, than in a similar group of non-jaundiced normal controls.

the advent of vascular spiders. Nevertheless, chronic and severe cirrhosis was the chief offender.

When this point in the study was reached, about four years ago, two explanations for the impasse were entertained. Either the vascular spider was evoked in liver disease only in certain susceptible persons, as a result, presumably, of a hereditary disposition; or the hepatic dysfunction underlying the phenomenon was neither measured by any of the commonly used chemical function tests nor indicated by specific clinical signs.

Some of the foregoing points will be illustrated by the following case histories of several patients with vascular spiders.

CASE REPORTS

Case 1. U-111347. C. W., a 50-year-old white male, had used excessive quantities of spirits during most of his adult life, having taken all available varieties of beverage and non-beverage alcohol. During the recent past his drinking had abated somewhat because he could no longer tolerate his former liberal allowance. Five years before his first admission to the hospital he had jaundice which lasted for ten weeks and kept him in bed. Troublesome nose bleeds had complicated this illness. He recovered with no apparent sequelae and was well for a year. He then had a second attack of jaundice which was associated with abdominal swelling. His family physician warned him against further drinking, but soon after recovery he fell into his usual habits. In spite of his alcoholism he was able to eat an adequate diet until a few months before his first admission to the Medical Service of the General Hospital, on January 3, 1939. Here he presented himself in a sorry plight; jaundiced, comatose, and nearly exsanguinated from bleeding esophageal varices. This crisis occurred shortly after a particularly prolonged spree at Christmas time.

Physical examination was notable for the complete picture of hepatic cirrhosis it revealed. The patient was in deep shock, with a rapid, thready pulse, low blood pressure, sweating and cyanotic extremities, which were cold and clammy. The color of the skin, a grey-green-yellow, indicated the presence of jaundice as well as hemorrhagic shock. His breath was strong with the disagreeable mousey odor of hepatic coma. Careful inspection of the skin disclosed a few small spiders. During a period of transfusions, as his red cells were restored towards normal, many additional spiders could be seen (Fig. 6). Other evidences of cirrhosis included a swollen, tense abdomen with demonstrable ascites and many collateral veins. There was edema of the legs and feet. When the ascites had been reduced by paracentesis the liver was found to be small and the spleen palpably enlarged. Even after the hemorrhage had stopped and the hemoglobin was restored, he remained in coma for several days, but finally rallied in spite of what had seemed inevitable disaster.

When he was convalescing his diet was made rich in vitamins and carbohydrate, although he was not given any concentrates or crystalline vitamins. When he was ready for discharge, six weeks after entry, it was found that his spiders had decreased in number from 16 to 7. Many of the smaller ones had disappeared leaving no trace. Where the larger ones had vanished a small area of atrophic skin, usually with traces of brown pigment, gave the only indication of anything abnormal.

Interval: In spite of the most urgent warning the patient resumed his custom of steady drinking, interspersed with sprees of more pronounced inebriety. This culminated in a relapse; his earlier symptoms reappeared, and he was brought to the hospital the day after the 4th of July in the same state as at the first admission, in coma and shock, jaundiced, distended with ascitic fluid, and vomiting blood.

Second Admission: The physical signs were much the same as on the first entry, although he was not so deeply jaundiced, nor were the hemorrhage and coma as severe.

There were no new spiders, but he had lost no more since discharge. With the same treatment he responded so rapidly that he felt well enough to sign out after 10 days.

Interial: During the next three months the patient left town, but his symptoms became so aggravated that he went to another hospital. Here the same findings were reported, and in addition his liver was observed by means of a peritoneoscope, which disclosed the diagnostic picture of hepatic cirrhosis, the liver being very small. When he returned to



FIG 6 Case 1. Cirrhosis of the liver. Picture taken 1-21-39. Several small vascular spiders may be seen; one to the right of the sternum in the second intercostal space, one in the jugular notch, one near the mesial end of the left clavicle, and the smaller, atypical lesions scattered over the face and chest. The lesion at the angle of Louis is a small acne pustule with its surface traumatized.

Cincinnati he was forced to stay in bed, except for visits to the out-patient clinic, where he was given mercurial diuretics and his abdomen was tapped. It became impossible to treat him in this manner and he was admitted to the hospital again on November 12, 1939, complaining only of great weakness and an enormously swollen belly.

Third admission: There had been a general decline in weight, a fact which became clear when the ascitic fluid was removed. The two pictures (Figs 6 and 7) indicate this and show several new vascular spiders on the face. The ones on the cheeks pulsed vigorously. By x-ray studies the presence of esophageal varices was substantiated. After two weeks of

supportive treatment the patient was allowed to go home. His condition was becoming worse, but the main problem was ascites rather than jaundice.

Interval: Because his other hepatic functions were not deteriorating as rapidly as the portal obstruction was developing, it was decided as a counsel of desperation to perform an omentopexy. For this the patient was admitted early in January, 1940, a year after his first visit to the hospital and seven years after the appearance of signs of beginning cirrhosis. He had mild jaundice and advanced ascites.



FIG. 7. Case 1. Cirrhosis. Picture taken 11-29-39. Two large, elevated pulsating spiders symmetrically placed above each nasolabial crease stand out prominently. Three new ones are seen in a line on the forehead. One has appeared above the inner canthus of the left eye. The lesions on the chest, not in sharp focus, are larger than they were 10 months before.

Last admission: Even with painstaking preoperative care, a liberal use of vitamins, and a high carbohydrate and protein diet, the patient could not be brought into good condition. The omentopexy was performed and he recovered from the first effects of the operation but died in coma, with moderate jaundice, a few days later. There were no measurable changes in his spiders.

Autopsy: The autopsy provided a second confirmation of the diagnosis of cirrhosis. The liver weighed 1375 grams and its irregular surface was studded with fine nodules. The spleen was fibrous and weighed 310 grams. Esophageal varices were demonstrated.

Comment: This man was observed during the last year of his life while remissions and relapses in his disease were occurring. Table 3 gives evidence that the advent of new spiders was not characterized by any striking change in the results of laboratory tests. No observations were made throughout a phase when spiders were increasing in size and number. Hemorrhage from the nose may have resulted from trauma to an angiomatous vessel in the nose, although this point was not established. This man went through an episode of severe bleeding later and observation at this time revealed only very sparse small spiders. The changes following transfusion make it reasonably certain, however, that he had larger lesions not evident during the critical period of his entry into the hospital.⁵ When the lesions regressed they left only a spot of atrophic or nearly normal skin, with or without pigmentation, as a mark of their former existence. Photographs made at two stages of the disease reveal some of the changes in the spiders.

TABLE 3
Laboratory data and spiders
Case 1

DATE	STERUS INDEX	BLOOD UREA NITROGEN	CO ₂ COMBINING POWER	PROTHROMBIN TIME	CHOLESTEROL	CREATININE	30 MINUTE BROM- SULPHALEIN RETENTION	A/G RATIO	VANDEN BERGH		SPIDERS
									Direct	Indirect	
1- 4-39	25	31	54	20	170	1.1	10	2.9/3.5	+	+	16 Spiders. None pulsating. Largest 3 cm. in diameter. Many faded within 6 weeks
8- 5-39	15	47									No change in spiders since discharge
11-12-39	8	17					15	2.8/3.3			Several new spiders, 2 pulsating (25 in all)
1-12-40	16	21	55					1.7/4.2	+	+	No change in spiders

Case 2. U-113422. C. R., a 38-year-old colored man, about a quarter of whose ancestry was Negro, was first admitted to the Medical Wards on January 15, 1939, with jaundice and ascites. He had been a heavy drinker for more than 10 years. In 1936 and 1937 he had been treated for syphilis, with arsphenamine and bismuth. About 6 months before he came to the hospital he began to grow weak and to have vague aches. Three months later he was forced to reduce his drinking because of vomiting, which was most pronounced in the morning. Somewhat later his abdomen grew larger and he became short of breath on trivial exertion. There were vague cramps in the lower abdomen. His sclerae were icteric, although he had not been aware of this before entry into the hospital.

⁵ Blanching and disappearance of the lesions are dependent on the changes in the cutaneous blood vessels associated with exsanguinating shock. Many of the spiders, although present, are invisible or difficult to see until the circulation is in a more nearly natural state. It is unlikely that very large spiders, several centimeters in diameter, could have developed in as short a time as 24 hours, although some do grow very rapidly and may reach that size in as short a period as ten days. In this patient, and in others whose spiders were watched before and during large hemorrhages, the lesions disappeared or became so faint as to escape detection unless the site had been marked.

Examination revealed a well developed but thin Negro whose light tan skin was noticeably yellowed, as were the whites of his eyes. The abdomen rose above the rib margin and flared in the flanks, but no collateral vessels were found. A hand's breadth below the costal border the smooth edge of the liver could be felt, and *percussion or light pressure* in this region caused some pain. The spleen was not felt. Hemorrhoids of large size were present. Spiders, 24 in all, were found on the neck and left shoulder, with one on the index finger of the left hand. The patient had noticed that they began to appear shortly after his health failed, six months previously, and had increased in size as well as in number during the progress of his illness. His icterus index was 33; both direct and indirect Van den Bergh tests gave strongly positive reactions. The serum albumin was 2.8 and the globulin 3.9 grams per 100 cubic centimeters of blood. Response to the Kahn test was positive.

Course: The patient responded rapidly to symptomatic treatment and his abdomen was tapped only once. After two weeks he was discharged with instructions to eat a nutritious diet and to stop drinking. His spiders did not change during the period in which he was under observation on the wards.

Although the diagnosis of cirrhosis was clear enough, it was impossible to decide what part alcohol, syphilis, or the treatment for syphilis played in his disease.

Interval: Soon after discharge the patient returned to his alcoholic habit, trying to make up for time lost in the hospital. The result was an increase in the severity of his symptoms, which brought him back into the hospital on February 16 for a *second admission* three weeks after he had been discharged. The physical signs had not changed except that two new spiders had appeared, one on each upper arm. While he was in the hospital he had a series of tarry stools. Special x-ray studies failed to indicate the presence of esophageal varices. The bromsulphalein test revealed a retention of 40% of the dye at thirty minutes. Other laboratory tests showed no significant deviation from those of the first admission.

Follow-up: The patient has been observed intermittently up to July, 1942. When first seen, seven months after his last hospitalization, three of the spiders had vanished, including a large one on the finger. During this period he had sworn off liquor with apparent success. Throughout the next three years his spiders gradually diminished in size and many now exist as an isolated red punctum with no branching radicles and no surrounding area of redness. Although he drinks at times he has reduced his intake and works regularly as a peripatetic electric repairman. No further signs of jaundice or ascites have appeared. Only 10 spiders can be found, even with photographs and diagrams to direct the search.

Comment: The presence of vascular spiders in a person with Negro blood has been reported only once, previously (153). The patient whose case we are reporting had noted the appearance of spiders during a period when the signs of cirrhosis were vague and non-descript. Two new lesions had appeared in typical form within a period of three weeks. In the first seven months after discharge from the hospital only three of the lesions disappeared, but the largest one was in this group. During the subsequent three years the spiders have faded away, leaving only 10 of the a former total of 26. Many observers have noted the presence of spiders before diagnostic evidence of hepatic disease could be found. Because of the not infrequent occurrence of similar lesions in apparently normal persons it is impossible to judge the importance of this finding if it is an isolated one. In the patients I have seen at a time when they had spiders before clinical hepatic disease had developed, the lesions have been numerous, while they are few in the apparently normal subjects.

Case 3. U-167715. W. A., a 44-year-old white man, was admitted to the medical wards on January 5, 1942, because of painless jaundice and ascites. He acknowledged that he had drunk excessively of beer for the past eight years, and in the latter half of this period had consumed an ever increasing ration of whiskey. This had resulted in a failure to eat properly for a long time. Recently the inconvenience of a swollen belly and digestive disturbances had become so annoying that he sought relief in the hospital.

Physical examination revealed a well built, heavy-set man who was not acutely ill.

The skin and sclerae were moderately yellow. His liver could be felt readily, presenting an irregular margin at the level of the navel. The spleen was not palpable. Ascites distended his abdomen, and small collateral veins were seen. There were several external hemorrhoids. Prominent vessels over the nose gave it a magenta color characteristic of the well established "rum blossom." Two spiders were found on his face, and several on the neck, chest, shoulders and arms, totaling 19. The palms were normal.

Laboratory tests showed an icterus index of 30, blood urea nitrogen of 14, prothrombin time of 20 seconds (control 16). Direct and indirect Van den Bergh reactions were positive. The serum albumin was 3.9 and globulin 2.6 grams per 100 cubic centimeters. Only 5% of the bromsulphalein was retained at the end of 30 minutes.

Course The patient remained in the hospital for two months, being treated with a high carbohydrate and protein diet supplemented with the B complex vitamins and yeast. During this time several of the spiders disappeared, only 14 remaining, and the nose became less red. The supplemental therapy was discontinued and the patient was subjected to a course of estrogenic therapy, following which his nose became red again and two new spiders appeared (one in the palm). A typical case of palmar erythema, which had not been present before, now developed. After this experiment had been terminated the patient went home and two weeks later all the cutaneous vascular alterations had regressed toward the normal, the palms faded, the nose became less red, the spiders were fading, and the skin vessels were becoming less apparent. This case has been reported elsewhere (17).

Comment This record is included because of the changes which took place in the vessels of the skin following estrogenic therapy. The possible significance of this effect will be discussed later.

Case 4 U 168816. A. H., a 53 year old white man, with one Indian grandparent, was admitted to the Medical Service of the Cincinnati General Hospital on February 2, 1942 because of jaundice of a month's duration. He was never a heavy drinker, rarely taking any beverage alcohol. His diet had been good in all respects. For about a year he had been growing weaker, although he did not stop working until two months before he entered the hospital. Edema of the feet was noticed four months previously. At about this time he had the first of a series of nose bleeds which had recurred at frequent intervals. Vague abdominal discomfort became focused about a growing lump in his right upper abdominal quadrant. He had been aware of a single cutaneous spider for many years but had had no previous jaundice or hepatic disease.

Physical examination Besides the obvious jaundice the most striking feature was the evidence of weight loss, emphasized by the high cheek bones and gaunt look. The left breast was slightly enlarged and tender. Fluid distended the lower abdomen and flanks, over which ran a meshwork of engorged collateral veins. There was a large, firm, mobile, nodular mass, visible and palpable in the right upper quadrant, extending 10 inches below the right costal margin. The spleen was also palpable. There were no hemorrhoids. The skin was marked with a number of vascular spiders of several types, which may be seen in the photographs (Figs 8-14). The large pulsating one on his left shoulder had been present for years. There was a faint palmar erythema which included the terminal phalanges of the fingers which also exhibited clubbing of the nails (Fig 10). During the course of his stay on the wards at a time when the patient was going downhill rapidly, an aneurysmal vessel developed on the conjunctiva at the same time that two new spiders made their appearance in his skin (Figs 10 and 13).

Chemical Studies The icterus index was 32, the urea nitrogen 12 mg. % and the A/G ratio was reversed, the albumin being 3.3 and the globulin 3.9 grams per 100 cubic centimeters. There was not much change in these figures during the month he remained under observation.

Biopsy Studies A section of the liver removed at an exploratory laparotomy revealed the presence of a hepatoma superimposed on cirrhosis. The large spider on the left shoulder was removed for study.

Course The disease progressed slowly. Ascitic fluid accumulated and was removed

several times. No new vascular spiders appeared at the site of the abdominal wound, the skin biopsy, or at the points of paracentesis. The patient was allowed to leave the hospital after two months and was sinking rapidly when last heard from.

Comment: Several items of interest are to be noted in this case. One is the long period elapsing between the advent of a spider and the occurrence of cirrhosis. Another is the fact that nose bleeds had occurred shortly before the patient's admission to the hospital. The differences in the sizes, shapes and contours of the several lesions, as seen in the photo-



FIG. 8. Case 4. Cirrhosis and hepatoma. This picture was taken a month after the patient was admitted to the hospital. It shows the two spiders on the left shoulder, the conjunctival aneurysm, and the slightly distended abdomen. Note the deep pigmentation of the nipples, and the questionable gynecomastia of the left breast.

graphs, are also interesting. The development of two new spiders and an aneurysmal coil of vessels in the conjunctiva is noteworthy. Association of digital erythema and clubbing of fingers has been pointed out elsewhere (17). Palmar erythema was also present. The emergence of a typical spider in eight days is illustrated.

Case 5. A. W., a 15-year-old white school boy, was admitted for the final time to the medical service of the General Hospital on November 25, 1941, having been observed for six and a half years in the clinics, and on the pediatric and medical wards.

Family History: Of interest was a story the mother volunteered, that she had had re-

peated nosebleeds at the time of the inception of puberty and that this tendency gradually disappeared after three years. An aunt died of hemorrhage from some unknown site. Several members of the family were examined but none had any angiomata of the spider type, nor was there any lesion of Osler's disease. There was no history of cirrhosis or of colitis.

Past History: This boy was the subject of careful study on the part of the house staff and numerous consultants. He first came under observation in the pediatric clinic in June 1935, where the cause of a chronic low-grade fever was sought. The fever subsided but remained undiagnosed. No spiders were seen in the skin, and the liver and spleen were

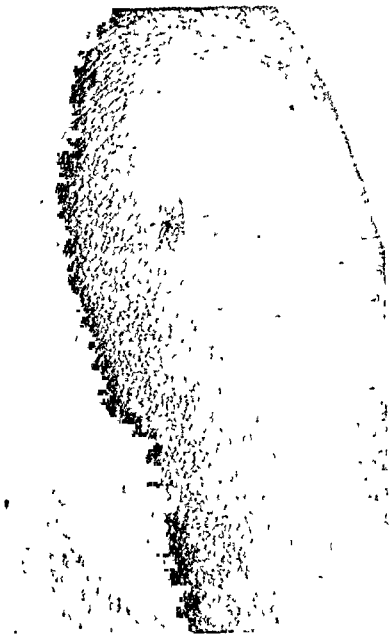


FIG 9. Case 4. Cirrhosis and hepatoma. A "close-up" of the left shoulder showing the two vascular spiders. The lower one, which had been present for years, pulsed vigorously, the upper one very slightly.

not palpable. This patient was examined in the clinic again early in 1938, when he complained of nosebleeds and somewhat later of blood in the stools. He was first admitted to the hospital in June 1938, when it was found that he had severe hypochromic anemia and a liver several inches larger than normal. Several typical spiders were seen, distributed over the forehead, left cheek, both arms and hands. The conjunctivae were injected. Most notable was the proctoscopic inspection which revealed five distinct angiomatous lesions, one of which had the same spider-like configuration as the lesions in the skin. Its size and proportions were also similar. During this stay in the hospital there were several nosebleeds and on two occasions fresh blood was passed per rectum. It was the impression

of those on the pediatric service that the patient had hereditary hemorrhagic telangiectasia, although a lone dissenter considered the condition to be cirrhosis with accompanying cutaneous spiders. Following his dismissal from the hospital the patient was treated in the pediatric clinic with small doses of iron.

All went well until August when he began to notice bleeding from the penis. He was again admitted on September 2, 1938. At first it was suspected that he might have mucosal telangiectases in the bladder, but instead there was an angiomatous lesion on the foreskin.



FIG. 10. Case 4. Cirrhosis and hepatoma. This picture shows the aneurysmal conjunctival vessel and the clubbed fingers

There was no more bleeding following circumcision. Otherwise the physical signs had not changed. Laboratory studies showed the same hypochromic anemia; a prothrombin time of 26 seconds, and reversal of the albumin-globulin ratio with figures of 3.8/5.7. On discharge from the hospital, iron therapy was again prescribed.

His third entry was occasioned by a severe nosebleed on December 20, 1938. The only additional finding of note was the presence of extensive meshworks of telangiectatic vessels in the nasal mucosa. The cutaneous spiders were unchanged, and proctoscopic examination

showed the same lesions in the rectal mucosa. The liver was thought to be a little larger. The patient was discharged after local treatment of the nose.

Visits to the clinic became less frequent. His mother noticed that the iron caused episodes of diarrhea which would end when this treatment was discontinued. The alternation of iron therapy and diarrhea persisted for almost a year.

The fourth admission occurred on December 11, 1939 when the main symptom was diarrhea which no longer ceased when the iron was discontinued. The stools often con-



FIG. 11 Case 1. Cirrhosis and hepatoma. Several typical small spiders on the back of the left shoulder and upper arm. Since this photograph was made without oil on the skin, it does not reveal the radicles clearly but gives a good idea of the natural appearance of the lesion.

tained blood but now for the first time the rectum was free from telangiectases. Of special note was the fact that all but four of the cutaneous spiders had disappeared whereas in the previous year there had been 13 characteristic ones. The liver was still larger, coming down slightly more than a hand's breadth below the ribs. For the first time the spleen was felt. Roentgen study gave suggestive though not conclusive evidence of esophageal varices. With transfusions and supportive treatment the patient improved and was sent home early in February 1940. All observers agreed that he had cirrhosis. At this time his weight was 93 pounds. When seen in the clinic on April 5, 1940, it was found that all the cutaneous spiders had disappeared, leaving faint traces of brown pigment and atrophic skin which could be found only by identifying the regions previously mapped on a chart. His hemo-

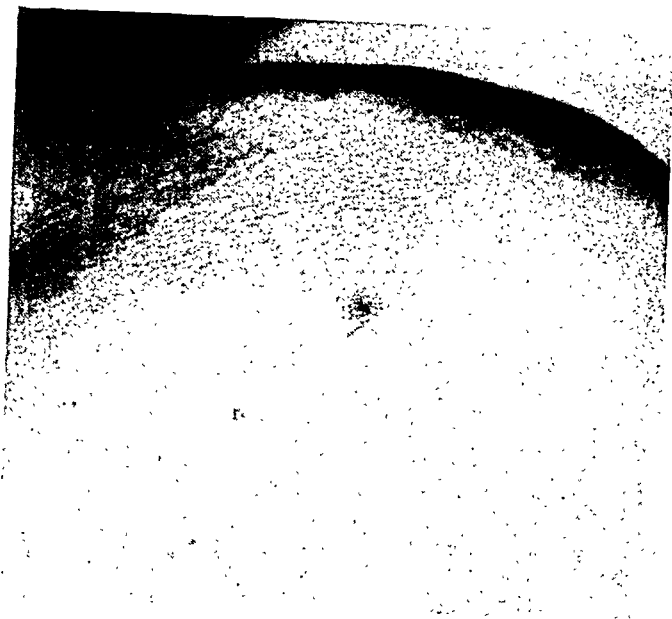


FIG. 12. Case 4. Cirrhosis and hepatoma. A typical medium-sized spider on the back of the right shoulder



FIG. 13. Case 4. Cirrhosis and hepatoma. This picture shows one of the new vascular spiders which had appeared along the left anterior axillary line eight days before. It was not present two weeks previously when the picture in Figure 8 was taken.

globin was 10.4 grams per 100 cubic centimeters. From May till September he continued to have frequent stools which were watery, light brown, flecked with blood and mucus, and foul smelling. At times clots of blood were passed. The number of stools varied from

eight a day to an uncountable, almost constant diarrhea. There was one episode of vomiting blood. He lost 17 pounds

The sixth entry to the wards was on September 11, 1941. X-ray and proctoscopic studies gave evidence of an advanced state of colitis with ulcers, sloughs and shreds of mucus from the colon which had become semi-rigid and pipe-like. Inspection of the rectum was difficult because of the tenderness and advanced maceration of the skin, but nothing resembling a spider was seen. None remained on the skin. It was remarked that physical and sexual development had progressed little for several years. There was almost no pubic, axillary or facial hair. The penis and testes were very small and the body generally stunted. The liver had shrunk so as to be barely palpable, and the tip of the spleen was felt with difficulty. The red count was 2.8 million, and hemoglobin 5.4 grams per 100 cubic centi-

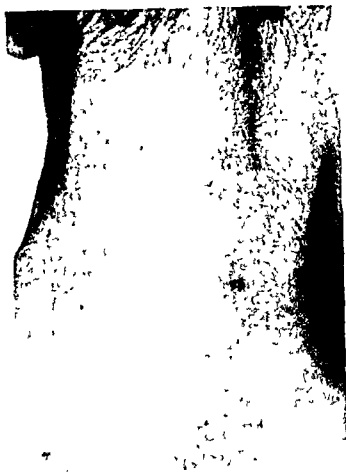


FIG. 14. Case 4. Cervical spider on the back of the neck with elevated shiny center, diffusely red area fading

spider on the back of the neck with radicles are seen but instead, a diffe-
resemblance to a pimple is clear.

meters. Transfusions, vitamins, and a high caloric, high vitamin diet low in fat brought about some temporary improvement. The patient went home for a few days but the distressing rectal incontinence and alarming asthenia brought him in for a final time.

The last admission was on November 25, 1941. There was no change except for a general deterioration. After elaborate efforts to build him up, an ileostomy was performed on December 6. For 12 days, to everyone's surprise, he seemed to improve, but an obstruction developed just above the ileostomy opening. A second operation was successful in overcoming this complication, but a week later the symptoms recurred and the patient died within 24 hours.

Autopsy confirmed the diagnosis of cirrhosis and ulcerative colitis. There was widespread peritonitis. Microscopic sections showed some unusual dilatations of the smaller portal vessels within the liver.

Comment: This patient's course illustrates many of the vagaries shown by vascular spiders. Protracted iron-deficiency anemia followed repeated bleeding, presumably from the mucosal lesions. This is the only instance included in this series of vascular spider occurring on the foreskin. The disappearance of vascular spiders in the presence of pro-

gressing hepatic disease is also of interest. The early confusion with Osler's disease is of importance, because it is possible that such cases have been responsible for the confusion of vascular spiders and hemorrhagic telangiectasis. Dilatation of small portal vessels in the liver has been observed before (115), although the nature of this change is obscure.

Case 6. 125847. W. T., a 61-year-old white man, was admitted to the General Hospital on August 1, 1939 for treatment of his enormously distended belly. The history of alcoholism dated back to the age of 27 years, at which time he had begun to drink whiskey every day. One year before admission to the hospital he had had a spell of jaundice and fever, but no pain, and had remained in bed for only a few days. His drinking had been steady and his daily quota of hard liquor ran over two quarts, according to his story. His food had been deficient in meats and vegetables, consisting largely of carbohydrates

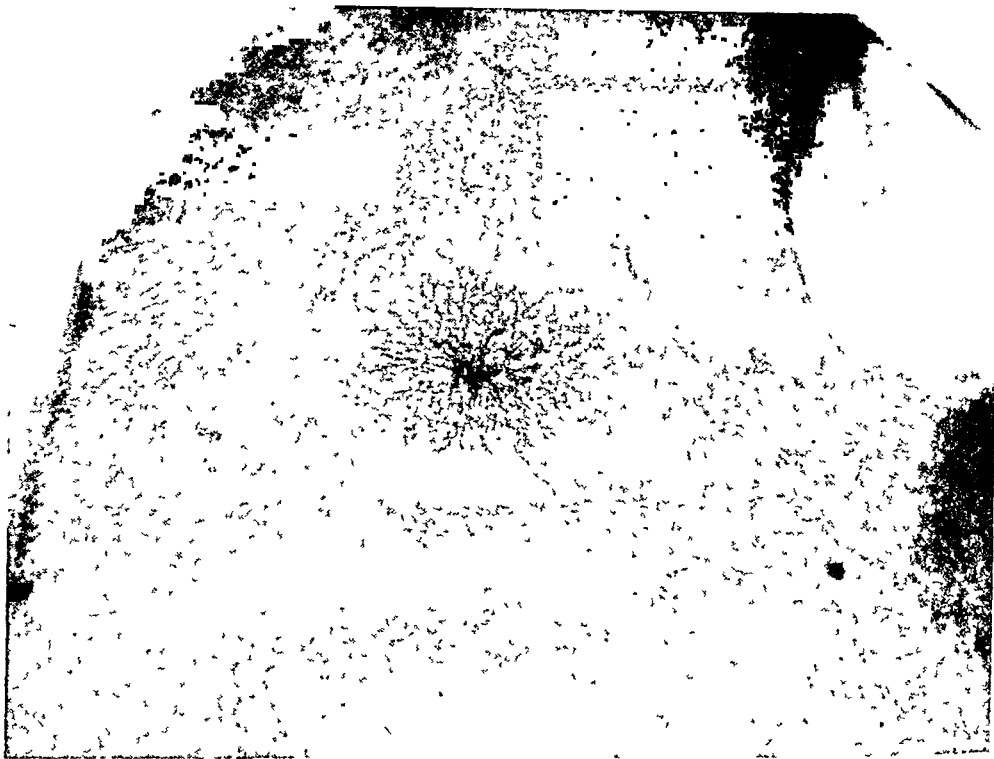


FIG 15. Case 6. Cirrhosis. This photograph shows the large vascular spider above the clavicle. Branches of the fourth and fifth order could be seen with a magnifying glass, but in this picture some of the apparent branches are artifacts resulting from the superimposition of several radicles streaming out in slightly different planes. Several additional small spiders may be seen.

and alcohol, although he probably ate more than the starvation ration he claimed as a diet. Some two months before he came to the hospital he noticed an insidiously advancing weakness and malaise which he associated with an increase in the size of his already ample abdomen. Shortness of breath confined him to his bed and a week before entry an irreducible edema of the ankles developed. He was unaware of his spiders or of the mild jaundice, and his mental state was such that his history was considered unreliable as to detail. It was found later that during the two months before admission to the hospital, he had been given several injections of neoarsphenamine by a private physician, who found that he had serological evidence of syphilis.

Physical examination was complicated by the semicomatose state of the patient. He was breathing with stertorous gasps, and the odor of hepatic coma was on his breath. There was definite though mild jaundice. Bulging of the flanks of his abdomen was extreme, and

a great accumulation of ascitic fluid was evident. There were extensive collateral veins over the lower abdomen. The liver was enlarged, hard and knobby. A few hemorrhoidal tags remained. The collection of cutaneous vascular spiders was notable for number, size and variety. Forty well-differentiated lesions were counted, and many incomplete ones were formed by aggregations of prominent vessels which marked the skin.

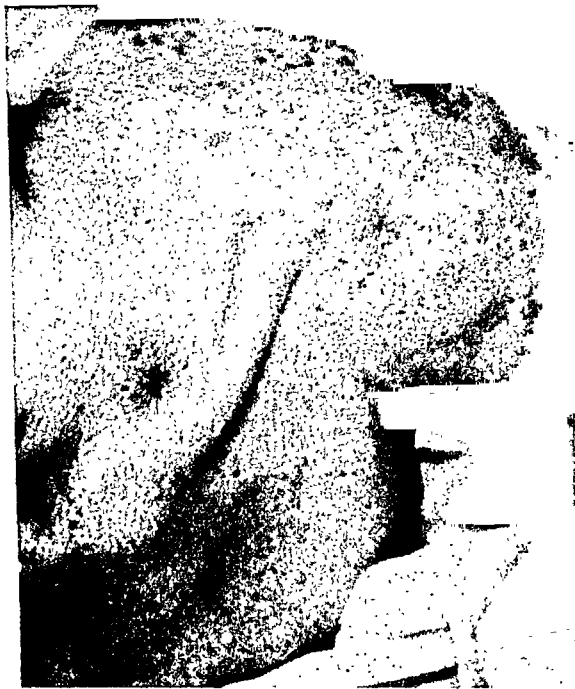


FIG. 16. Case 7. Cirrhosis of the liver. This and the two succeeding photographs were taken after the patient's second admission to the hospital, shortly before death. Several large, typical spiders may be seen above the left clavicle and on the shoulder. Smaller satellites appear toward the mesial aspect of the clavicle, and there are continuous anastomoses between some of them. Note the spotty pigmentation over the shoulder. The two large spiders were removed at autopsy for histological study.

Laboratory tests confirmed the clinical diagnosis of liver disease. The icterus index was 17; 50% of the bromsulphalein was retained 30 minutes after injection; and the serum albumin was only 2.6 grams, compared to the globulin of 4.9 grams per 100 cubic centimeters. Blood urea nitrogen was 27 mg. per 100 cubic centimeters. The Kahn reaction was positive.

Course: Following several abdominal paracenteses and supportive treatment, a temporary remission set in and the patient was able to go home for a few days. He lapsed into coma once more, was readmitted and died in a short time. No persuasion could elicit permission from the suddenly devoted family for an autopsy or removal of a spider. It

was apparent that this patient had hepatic cirrhosis, although the possibility of a superimposed hepatoma was not proved.

Comment: Two points deserve emphasis. There were three spiders on the legs, one on the calf, and two on the thigh. Spiders are very rare in this location, occurring in less than 1% of the cases in this series. The other unusual finding was the enormous size of the vascular spider above the right clavicle. It could be seen as well as felt, to pulsate. Easily visible radicles could be detected over an area 7.5 centimeters in diameter and the skin was definitely erythematous throughout a roughly circular area 10 centimeters in average diameter. Details of the macroscopic structure may be studied from the photograph (Fig. 10). I have seen only one vascular spider of greater dimensions.

Case 7. 153800. C. de B., a 36-year-old white male bartender, entered the medical service of the Cincinnati General Hospital on September 10, 1941, complaining of painless

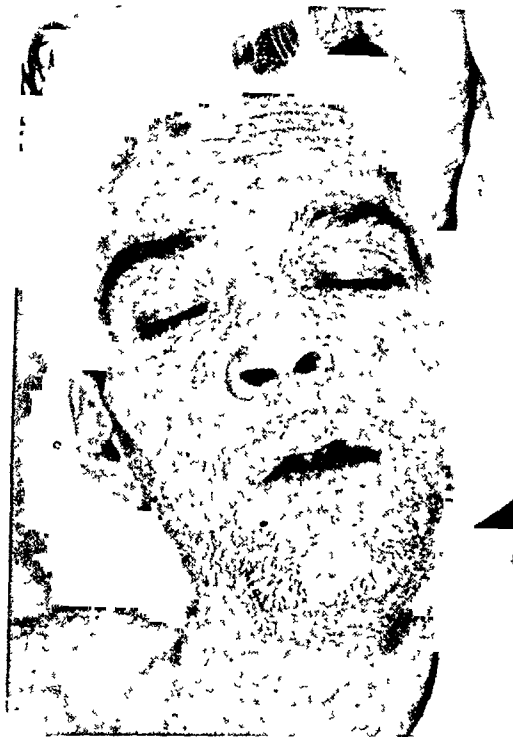


FIG. 17. Case 7. Cirrhosis of the liver. Several of the large, pulsating spiders with elevated centers present on the face may be seen in this picture. The details of the branches are not clear, but the actual appearance has been reproduced very well.

jaundice and ascites. He was accustomed to drink prodigious quantities of alcoholic beverages of any kind, supplemented with sundry non-potable forms of commercial products, including hair tonics, rubbing alcohol, various denatured alcohol and anti-freeze mixtures. His feats were acclaimed by his admiring companions whom he surpassed regularly. The history of alcoholism encompassed his adult life. For six years he had been given antiluetic treatment with arsphenamines and bismuth, more as the therapeutic urge struck his fancy than according to the physician's plan. His diet had been neglected badly. About a year before he came into the wards he noticed abdominal swelling, edema of the ankles, and jaundice, although he was still able to continue drinking on a somewhat reduced schedule. He visited the clinic at this time, and the diagnosis of cirrhosis was made. No cutaneous spiders were observed. During the two months before his admission to the house a recurrence of ascites and edema of the ankles was associated with difficulty in breathing on trivial exertion and he remained in bed most of the time. Mild jaundice was noted. These troubles progressed steadily up to the time he came into the hospital.

Physical examination of this chronically ill, emaciated man gave unequivocal evidence of cirrhosis. The abdomen was tensely swollen and not until some of the ascitic fluid was withdrawn did the bas-relief of collateral veins stand out prominently. Percussion of the liver indicated that it was much reduced in size and its edge could not be felt; nor



FIG. 18. Case 7. Cirrhosis of the liver. A. (Upper) An ordinary photograph of the right arm at the elbow, showing the body of a large spider near the center of the area surrounded by a superficial vein or venous plexus. B. (Lower) A picture of the same site, taken by infra-red photography. Note the failure of the spider to appear when this technique is employed. (Its location can be identified by traces of adhesive tape in the antecubital fossa.) This constitutes unequivocal proof of the arterial nature of the spider. (See text, under physiology).

was the spleen palpable. There was slight jaundice. The upper part of the body was flecked with vascular spiders. Other parts of the body were covered with "paper money skin." Edema of the lower legs was present.

Laboratory studies showed an icterus index of 15; a serum albumin of 2.7, globulin of 5.1 grams per 100 cubic centimeters of blood; and a positive Kahn reaction.

The course was favorable, and at the end of 10 days the patient went home "a.w.o.l."

Treatment had consisted of removal of ascitic fluid and a diet rich in protein and carbohydrate, poor in fat, with supplements of nicotinic acid, riboflavin and thiamin.

The *interval* between hospitalizations witnessed a return to his urgently interdicted alcoholism, and he was brought into the hospital, comatose, with ascites and jaundice, on March 7, 1942.

Examination revealed an abundant new crop of vascular spiders and an increase in the size of the old ones. Both types are seen in Figures 16, 17, and 18. Three spiders were on the usually uninvolved legs where none had been found during the first admission. A total of 83 typical lesions was found, an increase of 40 over the number found on the initial admission. Palmar erythema was now present. Among the numerous chemical studies, 40% bromsulphalein retention existed 30 minutes after injection, the icterus index was 21, and blood urea nitrogen was 40 mg. per 100 cubic centimeters. The albumin-globulin ratio was substantially as before. The patient failed rapidly in spite of the vitamin-dextrose treatment. He died in coma a few days after admission.

Autopsy confirmed the diagnosis of advanced atrophic cirrhosis with the liver divided into two small nodular lobes by bands of fibrous tissue. The spleen was small and fibrotic. Many of the spiders were removed for serial section and histological study.

Comment: This case was notable for the large number of spiders, their rapid increase in size and number, and their unusual distribution. Together with the palmar erythema, the red areas of the skin involved a substantial portion of the body surface, perhaps as much as one-fourth.

THE VASCULAR SPIDER IN PREGNANCY

Review

So far as I have been able to determine, the first observation of spiders appearing during the course of pregnancy was recorded by Corbett in the *British Journal of Dermatology*, in 1914 (52). He stated that he had seen spider angiomas appear in the skin during pregnancy and disappear entirely after its termination. This note has remained in oblivion since its interment.

Fibroma molluscum gravidarum, which was carefully studied and pictured by Bricker in 1906 and 1913 (33, 34), is possibly a related phenomenon.⁶

Ward (183) has written of "multiple pigmented warts" in pregnancy, but neither he nor Brickner made any mention of pulsation. It is improbable, however, that it was specifically sought. Brickner's second article (34) contains speculation about the possible relation of the lesions to glands of internal secretion.

⁶ Although this lesion is distinct from the cutaneous arterial spider, there is much similarity between it and an unusual form of spider not described in the literature, which I have encountered in two pregnant women who had typical cutaneous spiders in addition. It was characterized by prominent elevation, a warty or gristly texture, and a core consisting of a coiled central artery with definite pulsation. The alternate fading and flushing could be seen beautifully by depressing the surface with a glass slide. In both instances the atypical lesion appeared and disappeared simultaneously with those of the usual variety. Unfortunately, I was not able to persuade either patient to part with her strange stigma and so can only speculate about its structure. Never having seen the eruptive *fibroma molluscum gravidarum*, it is not possible to say whether the lesion described above belongs in this category or is something entirely different.

I have observed a pronounced erythematous change in and around ordinary pigmented moles during pregnancy in women simultaneously marked with typical vascular spiders. In one case pulsations could be felt. This erythema and the associated vascular spiders faded simultaneously post partum.

The next note on cutaneous spiders in pregnancy was presented by Zeisler (191). He was impressed with the possible rôle of syphilis as a causative agent. A more detailed description by Konrad (108), in 1925, called attention to the appearance of telangiectases on the face, neck and arms during the second month of pregnancy. This is the first emphasis on the distribution so characteristic of the acquired cutaneous spider in pregnancy as well as in disease of the liver (See Figures 1 and 2). The abrupt fading or vanishing of these marks in the postpartum period was observed. In the next year a similar finding was reported in a woman who had a pituitary tumor (7), and the possibility was considered that an endocrine disorder might be responsible for the skin lesion. Two examples of spiders in pregnancy were encountered by Urbach (181), who described the vascular lesions in detail. They vanished shortly after the end of pregnancy.

The first indication of a possible familial tendency was pointed out by Gougerot and Meyer (85), who observed the appearance of typical spider-like angiomas during the fifth month of pregnancy in four consecutive gestations, in a woman whose two sisters had also acquired spiders during pregnancy. Because of the history of syphilis in the family, they believed the lesions to be stigmata of hereditary syphilis. Distribution on the neck, arms and hands was noted. There were no mucosal lesions and no tendency to bleeding. No comment was made regarding pulsation.

Another report (149) described a case in which spiders were not present during the first and second pregnancies but appeared in the third month of the next pregnancy, occurring on the neck, chest and arms. The paper included a description of spiders of several varieties and sizes, with the larger ones typical in shape, having an elevated central boss and a peripheral anemic halo. The authors believed the distribution was related to the cutaneous nerves arising from the brachial plexus.

Forman (71) described a case in which the woman acquired spiders early in the second month of each of eleven pregnancies, all of which ended disastrously with delivery of a stillborn fetus before term. The spiders faded rapidly within a week after labor. He, too, believed that an endocrine disturbance was responsible. In addition, the coming and going of cutaneous spiders concurrently with the waxing and waning of symptoms in a patient with peptic ulcer was noted.

Vignes, Hanoun and Vial (181a) have reviewed the European literature on spiders in women during pregnancy and have recorded their familiarity with this innocuous phenomenon.

Walsh and Becker (182) in their monograph on erythema palmare and nevus-araneus-like telangiectases gave full description of six cases in which vascular spiders developed during pregnancy (in four, palmar erythema was also present). In some of the patients spiders had been present before pregnancy. Those in whom they appeared during pregnancy observed their advent anywhere from the third to seventh month. Spiders tended to parallel the palmar erythema in the time of onset and fading, but there were some exceptions. These authors discussed the number, size, configuration and distribution of the vascular spider.

and for the first time arterial pulsation was looked for and found in the spider of pregnancy. Their investigation included inspection with the capillary microscope and histologic study. A low-power view of one of their biopsy specimens gives an excellent idea of the two types of vessels encountered, the thick coiled stem artery in the subcutis branching directly into "veins" of comparable size.⁷ These authors have in preparation a more detailed description of the finer histology of their serial sections, a publication which is awaited with interest. They did not find any evidence of hereditary tendency except in the cases presenting palmar erythema, nor did they see any indication that the spiders had followed the often evoked "minor trauma" such as mosquito bites, pinpricks and the like. There was no incrimination of syphilis or disease of the liver. They believed the most probable cause to be some endocrine disturbance. Newman (134) has made the most specific statement regarding the cause, which he believed to be an increase in blood volume plus the effects of the hormone progesterone.

Observations

The neglect of the vascular spider by obstetricians is surprising since this lesion is a cosmetic nuisance occurring in pregnancy often enough to attract attention. Little systematic investigation of it has been recorded, however. The cases reported in this paper number 41. Some were seen casually, but enough have been studied with care to enable the writer to form a general idea of their prevalence, and of their striking changes during and after gestation.

It is uncertain when the spider makes its appearance in pregnancy, but my own observations indicate that most women who have them first notice their presence at some time between the second and the fifth month.⁸ This agrees with the data in the literature cited above (71, 85, 108, 149, 181, 182, 191). Usually spiders are thought to be pimples or acne lesions, and many women traumatize them, occasionally causing a severe hemorrhage, to their surprise. Oftener they are covered with face powder. Rarely they are feared as a manifestation of some malignant disease, or dreaded under the mistaken notion that they are a token of syphilis.

⁷ This they termed an arteriovenous anastomosis, but did not point out that it differs from the true arteriovenous anastomosis in having a multitude of "veins" branching from a central artery, and in the continuation of these "veins" into a capillary bed before the blood is conveyed away in true veins.

⁸ One very striking exception to this general rule has been observed by the wife of a colleague whose interest in spiders is both personal and general. She observed vascular spiders on her face and arms about the middle of the first pregnancy. These faded soon after the child was born and were entirely gone two weeks post partum. In a second pregnancy, for which the date of conception was certain, a spider on her face suddenly reappeared 10 days after the date of conception, and three days before the menstrual period was due. From this she made the diagnosis of pregnancy, which later was amply confirmed. This lesion enlarged slowly throughout gestation, and others appeared later. It was lost to view three days after delivery although it could still be felt, but no trace remained on the sixth postpartum day. This spider did not reappear in a third pregnancy, although many new ones were seen.

The habit of the vascular spider in pregnant women is to enlarge slowly until term. New ones may appear at any time during the second and third trimesters, and those already present tend to increase slowly in size. There is an abrupt decrease in size and number at, or a few days prior to, the time of delivery and during the ensuing ten days or two weeks. The smaller ones disappear without leaving a trace, and the larger ones either diminish in size or vanish during the period of uterine involution. These residual spiders often undergo a gradual decrease in size and number (for at least three years after pregnancy) which at length leaves the skin clear. Some persist.

TABLE 4
Percentage distribution of spiders in hepatic disorders

	Percentage
Face.....	10.0
Ears.....	0.3
Neck.....	12.5
Shoulders.....	17.5
Upper arms.....	17.9
Lower arms.....	3.4
Hands (dorsum).....	1.8
Hands (palms).....	0.1
Fingers.....	0.4
Thorax (front).....	28.1
Thorax (back).....	7.5
Abdomen.....	0.2
Buttocks.....	0.1
Thighs.....	0.1
Feet and toes.....	0.1

Distribution of 1720 spiders in 91 cases of hepatic disorder. The figures on which the percentages were based represented the maximum number present at any time. The greatest number of spiders seen in a single subject was 124. Several persons had but a single lesion. The average number was 19 spiders for each subject.

There are slight differences in the distribution of these lesions in pregnancy as compared with other conditions. This may be seen in Figures 1-5 and Table 4. Too much weight must not be placed on these observations, however, as they are relatively few and in many cases not complete.

There is a strong tendency for vascular spiders to become established when pregnancies are repeated at short intervals. In such cases a spider may grow to a larger size with each succeeding pregnancy, and fade only partially in the interim. Because of shortness of the study it is impossible to say whether they become permanent, or gradually fade away after termination of the child-bearing period.

I have noticed a few instances in which vascular spiders occurred in the infants of mothers who had acquired similar lesions during pregnancy.^{*} This is not invariably true, nor does it necessarily follow that one of the parents

^{*} This has occurred in children of both sexes.

will be found to have spiders, when they are present in a child. There appears to be an hereditary factor in many cases, however.

Palmar erythema may be associated with the vascular spider in pregnancy, and in some instances may be very well marked (182). It has been unusual in my experience but has not always been looked for.

The morphology and physiology of spiders in pregnancy do not present any essential distinction from those of the other types discussed. The location, pulsation, color, shape, size, warmth and other factors appear to be substantially the same.

When vascular spiders were observed to appear during pregnancy it was supposed that some toxemia or hepatic disorder was imminent, or smoldering; but in these patients no untoward episode marred the course of an uneventful pregnancy. The lesions vanished or faded during the early postpartum stage. Therefore it was natural to suspect that the advent and disappearance of these small subcutaneous arterial lesions bore a relation to the endocrine tides whose normal ebb and flow is so spectacularly altered during and after gestation. The time-relationship suggested placing the blame on estrogenic substances or at least on the 17-ketosteroid hormones, for the estrogens are at a higher level in the blood during the period of pregnancy when the spider is likely to blossom forth (13). Since there is no general agreement regarding the significance of urinary estrogen levels as a gauge of the total circulating estrogens or the rate of their liberation into the blood stream, the hypothesis suggested (15, 16, 17, 18) did not have any study of endocrine metabolism to support it.

Nothing in the persons studied here has indicated a relationship of these spiders to hepatic disorders, malnutrition, alcoholism, or any of the toxemias of pregnancy. Only one of the 41 women had ever had jaundice. In several cases the women were certain that spiders had antedated pregnancy, even though they had enlarged or become more numerous during its course; and there is no reason to doubt this observation. Much more information is needed on the exact time of the appearance of spiders in pregnancy, the suggested endocrine back-ground, and also the tendency to predisposition and familial occurrence.

THE VASCULAR SPIDER IN PERSONS WITH VITAMIN-DEFICIENCY DISEASES

Review

The vascular spider has never been described as a stigma of any vitamin deficiency disease. No reference to it as such appears in the medical writings on pellagra recently reviewed (19). There are a few remarks on telangiectases, however, and spiders may have been included under this classification. Majocchi (121) observed telangiectasis in alcoholic pellagrins in 1899; and the suspicion is obvious that cirrhosis and pellagra may have resulted from addiction to alcohol. The changes in the vessels of the skin may thus have been secondary to hepatic dysfunction. Marie (1910) mentioned a pellagrous woman "covered with telangiectases," without further comment (122). Fearnside (66) wrote a paper entitled "Telangiectases in children in association with wasting and protracted diarrhea" (1912). Some of the children had complicating deficiency

diseases, but there was no evidence of hepatic disorder. One may surmise that some of the lesions described were indeed vascular spiders since Fearnside commented on the same phenomenon in adults with cirrhosis. Alessandrini and Scala (4) described a woman with pellagra who had "venous ectasis on the nose and cheeks," but did not elaborate further. These brief notes, buried in discussions of other topics, constitute the only record of telangiectasia in vitamin-deficiency diseases. That they have been noted casually may be significant. Such comment had faded from contemporary medical literature on the subject until recently (15, 16, 18, 26, 27, 28), when it was revived owing to a possible relationship between these diseases and to endocrine function.

Observations

Data collected on the persons studied contain no decisive evidence by which to differentiate the vascular spider of normal persons and that encountered among the ill nourished folk seen in the Nutrition Clinic in Birmingham, Alabama, during 1940-41-42. Spiders have been observed in association with angular stomatitis, conjunctival and corneal vascularizations (riboflavin-deficiency syndrome) more often than with dermatitis, glossitis (nicotinic-acid deficiency) or peripheral neuritis (thiamin deficiency). In a number of instances they increased in size or number during the season of exacerbation of the associated deficiency syndrome. Often, however, there was no parallelism; and in two subjects spiders disappeared at the time when the symptoms of the vitamin deficiency were growing worse. Some new spiders appeared during or after successful revival of health following restoration of specific vitamins and other factors lacking in the diet. By far the greatest number of patients showed no change in the spiders throughout the three seasons during which they were under observation, regardless of the clinical course, the nutritional status, or the treatment of the patient.

A familial tendency to vascular spiders was strongly marked in the 120 Birmingham subjects. In 58% of those whose families were adequately examined, spiders were found in parents or siblings. They had been *observed* by the patients in only 13% of the cases so that a negative history is to be looked upon with some suspicion, unless verified by inspection of the persons under consideration. It is difficult to reconcile the familial tendency with the belief that vascular spiders are in some way a consequence of malnutrition, unless they be caused by a prolonged action operating over generations. Perhaps it indicates a somatic weakness which is also manifested by a susceptibility to the damage caused by specific dietary deficiencies, although there is no cogent testimony favoring this idea in the patients studied. That typical cutaneous vascular spiders were found in approximately 10% of all patients thoroughly examined may not be of great significance; the rate in "normal" persons also may be higher than generally supposed. Since no study was made of a cross section of normal persons of the racial stock and environment from which the clientele of the Nutrition Clinic was drawn, there is no evidence for or against a theory of hereditary tendency. The only material for comparison, that

observed in routine physical examinations of more than a thousand men between the ages of 21 and 28 years (*Selectees for the Armed Forces*) revealed one or more vascular spiders in 5.6 per cent. Males in the third decade of life are represented with singular rarity in the Birmingham group, so that this comparison is hardly valid.

There are several features of vascular spiders as seen in patients with nutritional deficiency disorders which call for comment. They were much fewer per person than in patients with chronic disease of the liver. Ordinarily they were small, having only a few visible branches and a small erythematous macule. Few could be felt to pulsate although occasionally pulsation was very forceful. The pressure needed to obliterate them, as determined by means of the capsule technique (see Physiology), was in the same range as that recorded for spiders in hepatic disease, although the average of the recordings in nine persons was 10 mm. of Hg. below that for the group with cirrhosis. A difference in distribution was found (Figs. 1-5) with a higher proportion of spiders on the hands and arms and fewer over the trunk than in subjects with hepatic disease or pregnancy. In no single case was a lesion found below the level of the diaphragm, and they were very rare on the trunk. The distribution of vascular spiders also differed among children, adolescents and adults (Figs. 3, 4, and 5). Between the ages of 1 and 10 there was a preponderance of lesions on the back of the hands and arms, with relatively few on the face. After the age of 20 the face and neck were involved predominantly. In adolescents the distribution was intermediate, striking a fair average between the two extremes. The meaning of this phenomenon is puzzling. It would be interesting to know whether these children will lose some of the vascular spiders on the upper extremities and acquire new ones on the face and neck as they grow older. I have been able to find no report on the exact distribution of spiders, or other telangiectases or angiomas, according to age groups. Certainly there is no analogy between this finding in deficiency diseases and conditions in chronic hepatic disease, for in the latter the same distribution obtains in the young, middle-aged and old (13).

The part played by multiple deficiency of the B-complex vitamins in perverted function of the liver in man is mostly unexplored. Several experimental animals suffer hepatic disorders, even fatal ones, when deprived of their ordinary requirements of certain vitamins (103). Because a diet rich in the B-vitamins and high in carbohydrate and protein has proved to be efficacious in treating human cirrhosis (148), it has been suggested that cirrhosis belongs in the category of the deficiency-disease syndromes. Alcoholic pellagra is believed to be caused by a reduced intake of the dietary factors which ordinarily prevent pellagra, for vitamin-free alcohol does not carry precursors of enzymes to regulate the metabolic fire it fans. The alcohol addict who eats heartily and with regularity does not get pellagra. Fatty livers were found more often than could be explained by mere chance in pellagrins who died in such numbers before the days of specific therapy (Harris, 121). Cirrhosis was not rare, but there is usually better reason to suppose that it was a contributory cause rather than a sequel or part of the pellagra syndrome. In endemic pellagra, cirrhosis is uncommon (19).

Aside from animal experiments, clinical observations suggest that some functions of the liver are crippled by prolonged deprivation of essential B-vitamins. A non-alcoholic pellagra may occasionally excrete large amounts of porphyrins in the urine, and this may be corrected by the administration of nicotinic acid, yeast or crude liver extract. Since porphyrinuria of this type is common in hepatic disease, this fact suggests that the liver is disorganized in some victims of advanced pellagra. The liver may be incapable of carrying on normal dextrose metabolism in pellagra. Jaundice and other indications of liver malfunction in alcoholic pellagra point to the same conclusion. The presence of fatty and otherwise diseased livers after death from pellagra adds its testimony. Finally, in cirrhosis the vascular spider may appear as a herald long before other signs of disease of the liver are present. For these reasons it is not possible to exculpate hepatic disease as the agent provoking the vascular spider found in association with well recognized deficiency disease.

The recent work of Biskind and Biskind (24-28) offers a tempting explanation for the occurrence of spiders in the group under consideration. In a series of experiments they have shown that estrogens are not inactivated, destroyed, or excreted adequately in animals deprived of an ample supply of B-complex vitamins. At the same time the metabolism of androgens is not compromised, so that there is an imbalance in the estrogen androgen ratio. Thus if it be true that a high level of circulating estrogens is causally related to the emergence of the vascular spider, these cases might be explained. Although exceptions were frequent, the vascular spiders in the malnourished patients did not regularly increase in size or number during a relapse, or decrease during a remission of the vitamin deficiency, whereas in cirrhosis the size and number of spiders *usually* varied directly with the clinical course of the disease, increasing before or during relapses and declining in number and size with a return of better health. In the patients with deficiency disorders cure of the disease was not regularly followed by change in the spiders (at least not within two years). The subject is one of importance because of the fact that many of the signs of deficiency of the B-vitamins are primarily or initially vascular, involving the small arteries, arterioles and capillaries (dermal erythema, glossitis, corneal and conjunctival vascularization). The lag following riboflavin therapy before the cheilosis or keratitis improves suggests that some intermediate step occurs. Improved hepatic regulation of the circulating hormones might act in such a manner.

One further point in this regard may be mentioned. Women with incipient pellagra have various menstrual disturbances, most frequently excessive bleeding between or during their menstrual periods (13). Amenorrhea is usual when pellagra is manifested by diagnostic lesions. No pelvic lesion has been demonstrated in such cases. This strongly suggests an endocrine disturbance, which might result from the liver's failure to keep the estrogen-androgen complex in balance.

Unless it can be established that the vascular spiders occurring in the Birmingham group have resulted from the evils of malnutrition accumulated over generations, it is difficult to account for them on the basis of an increase in

circulating estrogens, a common factor underlying those in pregnancy and in hepatic diseases. Until more observations are made or the liver is specifically implicated, the most reasonable conclusion is that these stigmata have no essential relation to the vitamin deficiencies with which they have been associated. If such should prove to be the case this group would fall into the category of vascular spiders occurring in well persons, without any of the usual predisposing causes.

THE VASCULAR SPIDER IN NORMAL PERSONS

Review

The emergence of the vascular spider as an entity separate from other small dilatations of the vessels in the skin of normal persons cannot be assigned to any specific time or author. Von Grafe coined the term telangiectasis in 1807, but did not remark on spider-shaped lesions. There is a large and fantastic literature on the subject of birth marks, or mother's marks, sometimes called "envies" because it was held that they resulted from some jealous passion of the mother during pregnancy. Others believed they were an indication of the noisome influence of a malevolent witch. Most of the records contain little about the exact appearance of the lesion but are devoted to speculation concerning the hypothetical forces alleged to have caused them. They are irrelevant here. An interesting discussion of various dermal vascular lesions may be found in the works of John Bell (21) (1826), although he was not above echoing some of the prevalent superstitions about them. Watson (186), writing in 1839, suggested a relationship between telangiectasis and arteriovenous aneurysm. He was the first to imply that a nevus or telangiectasis might be analogous in some ways to the post-traumatic arteriovenous fistula.

Besnier and Doyon (23), in a footnote to their translation of Kaposi, described *télangiectases pontués stellaires*, but did not discuss any clinical relationships. Marshall (125) reported the case of an infant who was born with many lesions, some evidently vascular spiders, many of which disappeared as the child grew older. The tendency for birth-marks to fade has been known since antiquity.

Among the vascular changes which have been found in association with spiders, the costal fringe has been noted especially by Osler (137) and Rolleston (161, 162). This must have been a commonly discussed phenomenon although I have not seen any specific mention of it prior to an article entitled "Vasomotor Ataxia" written by Solis-Cohen in 1894 (170). This author showed that the costal fringe was by no means confined to patients with cirrhosis but occurred in other diseases and in healthy subjects.

Jonathan Hutchinson, in his Archives of Surgery (99), reported a typical example of the vascular spider or *nevus araneus* in a healthy subject, and gave a scholarly description of its clinical features. He stated that such a lesion, dignified by the title of *Nevus Araneus*, was well known to the older English surgeons, but no reference was given and it has not been possible to track it

down. He also remarked that spiders pulsated, blanched with pressure, and filled instantaneously upon release. They were said not to occur in very young children but were found frequently after the age of five years. He had seen more in children than adults; and more in females than males, which he attributed to vanity. The tip of the nose was a favorite location, in his experience. He recommended cautery for their removal.

Fitzwilliams (70), in 1911, noted the centrifugal flow and also found that pressure on the spider caused it to fade. When the pressure was released the color reappeared first at the center and spread rapidly to the periphery. He believed that there was some peculiar relation to cutaneous nerves because of the aggregation of spiders along the distribution of some cutaneous nerves.

Sequiera (164) reported multiple telangiectasia in older persons without apparent disease. These lesions were similar to those described by Broq in patients with repeated attacks of hepatic colic. Sibley (166) was impressed with the symmetrical distribution of spiders in a 35-year-old woman who consulted him. After a time the lesions faded and ultimately disappeared. He made no note of a connection with hepatic disease or pregnancy.

A series of letters was published in the *Lancet* in 1916 concerning the significance of cervical capillary markings. Holt (97), Chisholm (42), and Hughes (98) believed that they were diagnostic of pulmonary tuberculosis, and somehow related to disease in the lung. Parkes Weber (142) and Riviere (159) thought they were not pathognomonic of tuberculosis and stated that at least half of the affected persons were healthy and normal. This argument is reminiscent of the polemic waged in America towards the end of the past century about the significance of angiomas as diagnostic hints in malignant disease, particularly that of intra-abdominal origin. It was finally agreed that these markings were neither characteristic nor diagnostic of such disease. One wonders whether the lesions in some of the cases which suggested this association were not examples of the acquired arterial spider in cirrhosis or carcinoma of the liver. This was inferred by Symmers (178), who finally quashed the argument with a soundly judged collection of case reports.

Becker (20) has given an excellent summary and review of the clinical aspects of generalized telangiectasia, classifying lesions as congenital or acquired, although he admits that there is some overlapping of the two varieties. He did not discuss the vascular spider separately but included some examples and case reports.

Williams and Snell (188) have commented on the spider in normal persons.

These few scattered references indicate that the vascular spider when occurring in normal persons has been recognized to be an insignificant stigma. No reason has been demonstrated for its sporadic occurrence; and no considerable attention has been given it. It is important because the common association of a similar lesion with hepatic disease (and pregnancy) has given rise to a widespread belief that it is diagnostic of some trouble in the liver, latent or obvious (37, 47, 184, 188).

Observations

Up to the time, in this study, when vascular spiders were found in normal children as well as in normal men and women, the notion had been entertained that the connotation of hepatic disease, past, present or future, was inevitable. With the gradual accumulation of a large number of cases in which no history or contemporary indication of such trouble could be elicited, the author became convinced—since he does not believe that the future holds promise that disease of the liver will be pandemic—that the vascular spider was not invariably a harbinger or omen of disordered function of the liver. This feeling was strengthened by observation of healthy and longevous families in which several members had been affected for many years.

Records of varying degrees of completeness have been kept on 107 persons with spiders in whom clinical hepatic disease, deficiency of the B-complex vitamins, and pregnancy, past or present, could be excluded.¹⁰ There were 57 females and 50 males. Forty were between the ages of 20 and 30 years, and 23 were children under 10 years of age. The youngest subject with spiders was less than a year old, and the oldest almost 80 years of age.

The number of lesions in a single subject was small. The average was slightly over three, and the largest number in any normal person was nine. Most often there was but a single spider. This is in sharp contradistinction to their prevalence in hepatic disease, where they may be myriad, or in pregnancy, where they may be plentiful.

The radicles in many of the vascular spiders found in normal persons are fewer in number and smaller in size than those in the spiders occurring in hepatic disease or pregnancy. Often the lesion appears as a red area about the punctum, with no legs. In a few instances anomalous forms occur in addition to the more typical ones. Pulsation has been found in a high proportion of the lesions. The pressure needed to obliterate them is in the same range as that determined in the other lesions studied (see Physiology). In the few cases in which other parts of the skin were examined with a high-power hand lens or dissecting microscope the results have been divided about equally; in about half the cases there were widespread changes in the cutaneous vessels, while the others revealed none. Distribution follows the general pattern noted in other conditions (See Table 4 and Figs. 1–5). The face and neck are most frequently marked with spiders.

The age at onset is variable. A number of lesions were first noted at about the age of puberty, but whether this was the true epoch of origin or merely denotes a developing self-consciousness is undetermined. They are frequent in young children, and in some may truly be called birth marks.

Inexplicable changes in size, even complete disappearance with subsequent recrudescence, have been noticed. The natural history may include a slow waxing and waning, months or years being necessary to complete a definite

¹⁰ No tests were carried out to exclude latent hepatic disease or secret alcoholic addiction, but the subjects were generally regarded as perfectly normal. The normality of this group can be established only by following the subjects for the rest of their lives.

cycle. In the absence of measurement or photographs it has not been possible to discern any rhythm of change.

THE VASCULAR SPIDER IN MISCELLANEOUS CONDITIONS

Review and Observations

Notes concerning the occurrence of typical cutaneous vascular spiders have appeared sporadically in medical reports on a multifarious and nondescript array of diseases. In many of the cases the presence of the spiders may have been merely coincidental, but it is impossible to eliminate a common cause when the pathogenesis is unknown. Spiders are said to occur in *xeroderma pigmentosa* (Crocker). Osler (135, 136, 137) has recorded instances in which spiders together with the more common mat-like telangiectasia occurred in x-ray scars. He also mentioned their occurrence in *scleroderma*. It is possible that Milbradt (130) was describing the same lesion, although the diagnosis of the condition he was discussing is obscure. Spiders have been noted in *rheumatic fever*, although Keil (106), in his survey of the rheumatic erythemas, did not separate them from a nonspecific telangiectasia. In my experience with vascular spiders occurring in rheumatic fever, these lesions have been seen in victims of chronic rheumatic valvular disease only when clinical signs of cardiac cirrhosis were present.¹¹ They may be presumed to have the same cause as in other forms of hepatic cirrhosis.

In victims of *Cushing's syndrome* one occasionally sees, in addition to the spectacular purple striations of the skin, various aberrations in the minute cutaneous vessels. I have seen one instance of typical vascular spider in this syndrome, in a case in which there was no clinical sign or symptom of hepatic disease. It is of interest that Friedman (74), in 1921, emphasized the occurrence of erythema and telangiectasis of the face in this condition, and Cushing (55) remarked upon it in describing one of his cases, although neither specifically noted spider or star-shaped lesions.

Vascular spiders are very uncommon in *Graves' disease*. Only one case has been observed among the fairly numerous examples of thyrotoxicosis encountered in the past five years. This example was noteworthy because the patient knew that the spiders had appeared many months after signs of severe overactivity of the thyroid had been observed. Following iodine therapy and subtotal thyroidectomy, the metabolism returned to a normal level, and after several months the spiders vanished. Unfortunately no tests of hepatic function were performed. The rôle of thyroid hyperactivity in damaging the liver has been discussed by Berk and Goldburgh (22), who concluded that hypovitaminosis-B was a factor. It was thought that this case of acquired vascular spiders in thyrotoxicosis was unique but a search of the literature has revealed that at

¹¹ The one exception to this rule was in a case in which several small red nodules appeared during an exacerbation of rheumatism. Although they were originally believed to be rheumatic nodules, they later developed the characteristic star-shape of vascular spiders, and after several months disappeared. This is the only time I have seen spiders develop under such circumstances.

least one other example has been reported. Hyde (100), in a paper entitled "Telangiectatic Lesions of the Skin Occurring in the Subjects of Graves' Disease," written in 1908, presented an extensive review and reported many cutaneous vascular disturbances, among which was at least one perfectly typical vascular spider. This article attracted some attention among dermatologists, who still refer to it, but it seems to have escaped the notice of authors of systematic treatises on the thyroid gland.

Spiders and Related Vascular Changes in the Mucous Membranes

During the first part of this study, no search was made for vascular spiders except in the skin. The lesson suggested by case 5 was not heeded. In the last 47 patients with hepatic disease and cutaneous spiders a search was made, and it revealed similar vascular aberrations in the mucous surfaces of 10. It is not possible to estimate the frequency of their presence in inaccessible regions, since the mucosal spider fades after death in the same manner as its dermal congener (13). Unless a careful endoscopic examination is made, one cannot state that they are not present simply because they are not seen post mortem. In this series of 10 cases, the mouth was affected in all 10, the nose in seven,¹² the rectum in three of the six examined proctoscopically, and the eye in two. (Eight patients had more than one site implicated.) In every case there were several telangiectases. In appearance, these vessels were irregular, rarely having the characteristics of a well defined central spot with radiating spokes. Pulsation was not evident upon palpation of the lesions in the buccal mucosa, soft palate, hard palate and gums. No lesions occurred upon or under the tongue, although a different form of telangiectasis frequently appears in the latter location, while the dorsum is often spotted with the characteristic lesion of Osler's disease (see Fig. 24). The coming and going of the mucosal spider paralleled that of the dermal type.

Mucosal spiders were seen chiefly in patients with a large number of skin lesions. No mucosal spider was detected in patients with hepatic disease without spiders in the skin. Verified hemorrhage from mucosal spiders has been confined, in this series, to those in the nose and in the rectum. In most cases of grave hematemesis, the presence of esophageal varices was demonstrated after convalescence or at post mortem examination. It is not inferred that severe or even fatal hemorrhage does not occur from small bleeding arterial spiders of the mucosae, but it has not been possible to establish such a case in this series.

Tortuous coils of redundant aneurysmal vessels in the conjunctiva have been seen in two instances, one of which is pictured in Figure 10. This change was seen to reach macroscopic proportions within a week. The gross morphology is strikingly different from the usual pattern of the dermal spider.

From these miscellaneous data, it is obvious that more mucosal spiders should be examined before conclusions are justified. The important fact has been

¹² This is in addition to a large number of patients who had engorgement of the network of vessels in the nasal septum, but no localized area characteristically involved.

established that macroscopic vascular changes comparable to those of the skin in the skin may develop in the mucous membranes. No information nor have we obtained any, on the histology of the mucosal lesions. 'relationship to hemorrhage is still to be defined.

PHYSIOLOGY

There has been some confusion concerning the nature of the vascular spasm. Palpation, pressure with a pencil point, or the use of a glass slide at once reveal the pulsation and direction of the blood flow. The bright red color suggests arterial blood. Nevertheless, there has been disagreement as to the nature of the lesion, whether it is essentially arterial, or venous, or both (20a, 32, 71, 111, 115, 125, 135). Some of the difficulty is doubtless a consequence of the histological picture which may include thick muscle-coated artery as well as thin-walled vessels resembling veins. The observations to be recorded here are the most part simply confirm and amplify those of French clinicians (32, 111, 113, 115, 173, 174) which were extended by Patek, Post and Victor (1935).

Pulsation: The pulsation imparted to the palpating finger by the central point or eminence is strong in the large lesion but may be felt with difficulty if at all, in the smaller ones. If a glass slide is placed over even small spider the pulsating center may be seen. By varying the pressure, the erythematous region may be made to contract from, or expand towards the blanched periphery. In very large lesions visible pulsation of the central eminence may be observed on close scrutiny.

Direction of blood flow: The centrifugal flow is demonstrated by placing pressure on the center, causing the legs to blanch. When the pressure is released the radicles fill instantly and the skin regains its red color.

Pressure: Patek and his associates (147) have published the only figure for the intravascular pressure of spiders. They found that obstruction of the brachial artery with a pneumatic cuff caused obliteration of pulsation in a patient on the arm when the pressure was raised to 85 mm. Hg. Pulsation returned when the cuff pressure, after further elevation, was lowered to the same level.

In our series, studies on more than 100 separate spiders in 27 persons have resulted in substantial agreement with these findings. The method used was also indirect but allowed observations to be made on the several compartments of the lesion. To the skin surrounding the spider a transparent cell capsule was attached firmly with collodion or rubber cement. A tube connected a mercury manometer was connected to a glass rod communicating freely with the interior of the capsule. Pressure could be altered at will by a rubber bulb connected to the manometer. The most satisfactory observations were obtained when the spider was situated over some flat bony surface, such as the sternum or forehead, although similar results were obtained in other areas provided the capsule could be kept in place firmly with counter pressure. Deformity produced in the skin included within the capsule and at the attachment edge introduced artifacts and obscured the changes in some tests.

When the spider was exposed to gradually increasing external pressure, fading began in the marginal part of the erythematous skin at a pressure bet

10 and 30 mm. Hg. In many cases this fading spread throughout the whole red area, causing the radicles to be silhouetted against a pale background. Into the newly blanched areas the larger legs of the spider pointed, in the form of fine red spokes. An ebb-and-flow pulsation could be noted in them. Centrally, where the skin was unblanched, it manifested the same change after the manner of an opening and closing iris. As the pressure was raised by slow increments, the skin was flattened against the underlying bone and the entire blush disappeared. There remained only the center and some of the large branches. These exhibited pulsatile ebb and flow as if small snake tongues were flicking in and out from the central eminence. When the pressure was between 30 and 50 mm. of Hg. the vessels were progressively obliterated centrally and were generally quite empty when the pressure was raised above 50 mm. Hg. At this point, the body of the spider appeared as a rising and falling boss, its red color contrasting brilliantly with the pallid background from which the blood had been squeezed. Further increases in the pressure caused the body to be obliterated intermittently, but between 50 and 70 mm. of Hg. there was usually a systolic appearance which faded with diastole. Between 70 and 90 mm. of Hg. the entire vascular pattern was obliterated. The reverse sequence could be seen as the pressure was reduced slowly.

The flexibility and elasticity as well as hydration of the skin, and the texture of the subcutaneous tissue had some influence on the pressure determinations. As a general rule the larger the spider, the higher the pressure required for the several stages of obliteration. In two instances in which the spiders had a central elevation of 3-5 mm., the boss was not flattened and blanched until 100 mm. of Hg. was reached. Pressure above this level usually distorted the skin and caused the capsule to ride up or break loose. With the subject supine, there were no differences in the pressure in spiders at various sites on the body (forehead, cheek, chin, clavicle, sternum, chest, shoulders, forearms, wrists, hands, and knees). No tests were made on mucosal spiders. The pulsations were more vivid and the range from beginning to complete fading greater when there was a high pulse pressure in the large arteries. The pressures in spiders in persons with liver disease, pregnancy, and deficiency diseases, and in normal persons were substantially the same. This indicates that more than a superficial similarity exists among the several classes of spiders. Confirmation of their identity must await histological study.

In three cases, observations made on the same lesions at intervals of ten months to a year gave identical pressures. In one instance, when a spider had faded and returned after several months (with a relapse in the cirrhosis), the pressures coincided with the first readings. In two instances pressure readings were made at short intervals during the phase of evanescence. In one, the pulsation could no longer be noted three days after the first measurement, and the radicles disappeared two days later; after two weeks, no mark was left. It seemed possible that the central artery had become occluded. In the other instance there was a gradual decline in the pressure required to obliterate the spider. Three determinations made over a two-month period revealed a fall in

pressure of 20 mm. of Hg. per month. Pulsations could not be detected 6 weeks later, when the only mark was a tiny red spot. No satisfactory observations have been made during the stages of enlargement.

Temperature: Determinations of cutaneous temperature over vascular spiders have been made with a dermotherm, both on the wards and in a constant temperature room (20°C). Tests were carried out on seven patients and more than 50 lesions. As was to be expected with arterial blood so near an exposed surface, the temperature of the skin over the spiders was found to be higher than that of the adjacent skin. The difference was greater when the environmental temperature was cool. The difference showed variations, ranging from a barely perceptible increase in the small spiders to as much as 3°C in large ones. The gradient of temperature difference between spider and adjoining skin was somewhat greater in the extremities than on the face or body. Increased skin temperature has been found also in palmar erythema (17).

Local injection of adrenalin and histamine: The intracutaneous or subcutaneous injection of these substances near a spider evoked the usual reactions found in normal skin. Blanching with adrenalin did not close down the larger vessels, whereas the erythema produced by histamine was more pronounced in the red area of the spider than in the adjacent skin. Similar results had been reported previously (147).

Changes with menstruation: In the past year two patients have been observed whose spiders increased in size three days before the menstrual period and remained large for two or more days of the period. In three other women the same event had been noted by the patients themselves but they believed that the change coincided with, rather than preceded menstruation. Many puzzling relationships of menstruation and skin disease have been reviewed by Bulkley (36). He made no reference to changes such as we have seen in vascular spiders, although similar periodic variations were reported in many dermatological conditions. A possible relation to some still unsettled questions regarding endometriosis might be mentioned (128). No studies were made to see whether the pressure within the spider underwent any variations during the menstrual cycle.

Distribution: Vascular spiders of the skin show a predilection for certain sites, and their distribution presents a regularly recurring pattern with minor variations. This has been discussed only in recent years (147, 173, 174, 184) although case reports indicate that the observation has been made ever since the first writing on the subject (189). In our material certain differences among the groups have been mentioned. Much more extensive data will be needed before the significance of these variations can be estimated. In general, spiders occur in largest number on the face and neck, and in decreasing frequency over the shoulders, thorax, upper arms, lower arms, backs of hands, and fingers. They are rare on the lips, ears, nail beds, palms, and very uncommon below the umbilicus where less than 1% have been found. They do, however, occur on the abdomen, foreskin, thighs, knees, foot, and toe in cases in this series (See Cases 5, 6, 7 and Figs. 1 and 2). I have not found them in the scalp, whether bald or

hairy. No differences in general distribution have been noted between males and females. A better idea of their locations can be gained from Figures 1-5 than from the tables showing the percentage distribution (4 & 5), for the regions selected are not comparable in area. Thus they appear most thickly on the neck and face, but the total number occurring on the upper chest and shoulders is larger.

Differences between the several groups, in respect to the distribution of the spiders, are indicated in the diagrams. The only group showing much variation at different age periods was that composed of the Birmingham cases, in which the arms, hands and fingers were preponderantly implicated in the first and second decades, while the face and neck were most frequently involved after the age of twenty. A larger percentage of the spiders occurred over the shoulders in hepatic disorders than in the other classes. Lesions on the hands in disorders of the liver and in normal subjects were rare, as compared to the very high incidence in those Birmingham subjects who were less than 20 years old. The scarcity of lesions over the thorax in the Birmingham material is in marked contrast to the findings in other groups, and the latter also reveal minor variations among themselves.

The meaning of these data is obscure. It is possible that in a much larger series of cases the discrepancies would be ironed out. Since no histological studies were made except in the case of patients with hepatic disease, it may be that some structural difference exists between the lesions in the several classes, of which we are unaware. The gross morphology, the similarity in physiological findings, and the location in the upper half of the body offer evidence that some common factor of relationship exists.

Of certain significance is the pattern of distribution over the body surface. Only after three years of painstaking search were any spiders found below the level of the umbilicus. These lesions were unmistakable, however, and pulsation could be detected in several of them. The cause of this arrangement has excited much speculation. Two investigators (65, 184), not having seen spiders in the lower regions, suggested that the drainage of the superior vena cava somehow determined their location. This seems improbable. There is no association with collateral circulation in the occurrence of spiders over the abdomen. It may be suggested more logically that the gradient of vascular tonus and temperature in the skin is in some way responsible. The number of spiders is greatest in areas where blushing is most intense. This territory also responds most vigorously, by vasodilatation, following the intravenous injection of histamine (114) or nicotinic acid (14). The vasomotor gradient of vascular tone in the subcutaneous arteries is high where the lesions are rare, and it is lower and very labile where they are numerous. If one suspects a humoral cause, the circulating agent might be in contact with the affected vessels for longer periods in areas where the tone was not so high and the flow of blood less rapid.

The relation of the distribution of these lesions to exposure to repeated minor traumata must be considered also, for their occurrence in the skin of the face, neck, and the back of the hand is frequent. Exposure to weather and to radiant

ergy may be a factor. This is strongly suggested by Brocq's work (35). If local metabolism were high in warmer parts of the skin, it might influence the segregation of spiders in warmer areas. Whether histamine plays any part is uncertain. A few experiments in which repeated injections of minute quantities of histamine or nicotinic acid were given to susceptible patients with cirrhosis, did not produce any new spiders. Evidence that local infection frequently responsible for the production of spiders has not been substantial (45). Altogether, the suggestions so far adduced are not impressive. The most promising speculation appears to be the one which relates the distribution pattern to the constant variations in vascular tone near the surface of the body. The pattern of density would thus be a function of the arterial vasomotorinus in the skin.

Infra red photography Since the vascular spider of the skin is brilliant red color, owing to the high content of oxyhemoglobin, the use of infra red photography suggested itself as a method of verifying the arterial nature of the lesion. Infra red technique has been used successfully to emphasize the outline of veins in complementary use—to obtain photographic obliteration of very red structures—has not been reported. In Figure 18 a comparison is made between an ordinary black and-white photograph and an infra-red photograph¹³ of an area with numerous vascular spiders. It can be seen at a glance that the spiders "disappear" when the infra red method is used. Several similar comparisons have yielded identical results. This adds confirmatory evidence of the arterial nature of the whole macroscopic structure of the spider. Not only does the central arterial portion vanish, the peripheral portion likewise disappears, the legs and radicles whose walls bear a closer resemblance to ordinary veins and venules than to arteries, but contain arterial blood.

Cross and Microscopic Structure

Systematic study of the histology, histopathology and histophysiology of the vascular spider has been neglected, although some texts on the histopathology of the skin offer brief remarks on the subject (117, 118). There has been much disagreement over the kind of vessel mainly implicated, also differences in opinion as to whether the spider is fundamentally an angioma, implying neoplasia, a telangiectasis, or both, and whether the affected vessels are veins or arteries, or both. This confusion has been greatly reduced by the work of Patek, Post and Victor (147).

Any effort to understand the aberrant structures under consideration must be based on knowledge of the normal blood vessels of the skin. One of the early students of this problem, Joseph-Louis Renaut, described and pictured a very characteristic nutrient artery supplying the skin, in his treatise on histology (154) which appeared in 1889. He noted the frequent occurrence of a small end artery in the subcutis which branched in radial fashion in one or more planes at right angles to the axial trunk and parallel to the skin surface. From the smaller branches nutrient arterioles spread in profusion, finally dis-

¹³ The filters used W W #87 deep red filter

tributing the blood to the capillaries. This small artery supplied a blunt cone-shaped region of skin and subcutaneous tissue. Blood from the region thus supplied was collected into venules in a meshwork surrounding it. The over-all architectural plan was similar to that in Mall's stellate arteries in the stomach and the stars of Verheyen in the kidney. Some such arrangement is usual wherever the blood supply to any tissue surface is abundant. Spalteholz (171) pictured similar vessels but indicated much freer anastomosis among the arteries of the deep and superficial layers. Stellate arteries were pictured by Krogh (110). It may be concluded that a stellate artery is a normal structure in the skin, but that it cannot be detected by inspection because of its small size.

The clinic provides two excellent demonstrations of this pattern of small cutaneous arteries. Both are accentuations of the normal vascular mottling which may be seen in exposed portions of the arms and legs, especially in young persons, during cold damp weather. In *livido reticularis*, a disturbance in vascular function makes the paler islands supplied by the terminal arteries stand out against a cyanotic background (1). The other condition, in which the reticulated network is pigmented, *cutis marmorata* or *erythema ab igne*, develops in regions exposed for long periods to heat (114). It has been possible in a few instances to find vascular spiders occupying the pale center surrounded by the darker reticulum of slightly mottled skin in normal persons or those with hepatic disease, but exceptions to this arrangement have been noted also (13).

Studies on the simple arteriovenous shunts and complex glomus bodies have brought to light facts relevant to the vascular spider (48, 49, 86, 87, 126, 127, 152). The simplest type of shunt is direct, with a single loop between an arteriole and a venule. The structure of the connecting vessel usually changes gradually from that of an artery to that of a vein (48, 49). On the other hand the true glomus is a complex series of vascular spaces with several alternate routes for passage of blood from artery to vein (126, 152). Its essential constituent parts include the afferent artery, the Sucquet-Hoyer canal, the primary collecting vein, preglomeric arterioles, and an abundance of nerves. The canal, a tortuous, bulbous, modified arteriole, empties directly into a vein. Its lumen is narrow and irregular, lined with endothelial cells in one or two layers, but without an inner elastic membrane. Muscle cells in the wall are interspersed with cuboidal cells whose nuclei are poor in chromatin. These "epithelioid" cells have poorly staining cytoplasm which gives a characteristic appearance. Non-medullated nerves are plentiful in the collagenous peripheral zone.

Glomus bodies are said to have an important function in temperature regulation (86, 87, 110, 152). Their peculiar concentration in the palmar and plantar pads, the nail beds, and the ungual phalanx of the digits, is noteworthy in connection with palmar erythema in which these regions become prominently marked with a more or less permanent redness associated with an increase in objective and subjective warmth (17).

Although Gilbert and Hirscher (78) reported on some of the histological details, Williams and Snell (188) appear to have been the first to suggest a relationship between the spider angioma and the glomus body. In their review

they presented excellent photographs of the large elevated pulsating spider, and in histological sections they demonstrated glomic tissue in the basilar angiomatous portion of the lesion. Their photomicrograph displays an example of a vessel whose wall shows on one side a mass of "epithelioid" cells and on the other a nearly normal muscular coat. The dilated, thin-walled, superficial vessels—the telangiectatic legs—may be seen clearly. It is unfortunate that they confused the spider with the vascular lesion characteristic of Osler's disease with its atrophic attenuated arterial wall.



FIG 19 An additional case of hepatic cirrhosis not included in the case reports. Multiple vascular spiders and pigment spots in a 46-year-old white man with longstanding jaundice and cirrhosis. The large fenestrated spot in the lower center was not a spider although it may have been the site of a previous spider. This is suggested by a similar vascular pattern in the large spider over the upper deltoid region.

Patek, Post and Victor (147) enlarged upon these observations. They stated that "the acquired type of spider . . . does not conform to descriptions of the congenital lesions," and ably demonstrated this fact in histological sections cut serially. Of interest was their discovery of two types of lesion. One consisted of an abnormally large artery rising from the subcutis, branching into arterioles, and terminating in capillaries. Except for its size it was identical with the artery of Renault. Two of their seven lesions fell into this class. The others were of the "glomus" type. In it "the afferent artery is of medium size, with a single layer of endothelium resting on an internal elastic lamella, and a media composed of circular muscle fibers. At the junction of this artery with the central vessel of the 'spider' the endothelium and the internal elastic lamella become separated by a thick layer of cells with elongated oval nuclei, abundant

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cytoplasm and indistinct cell borders. The nuclei are about as long and half again as wide as those of the smooth muscle cells of the arterial media. They have a more diffuse distribution of chromatin and are more widely separated. From the varying shapes and directions of the long axes of the nuclei the cells seem to run circularly, longitudinally, and diagonally. The internal elastic lamella and the media of circular muscle of the afferent artery continue into the

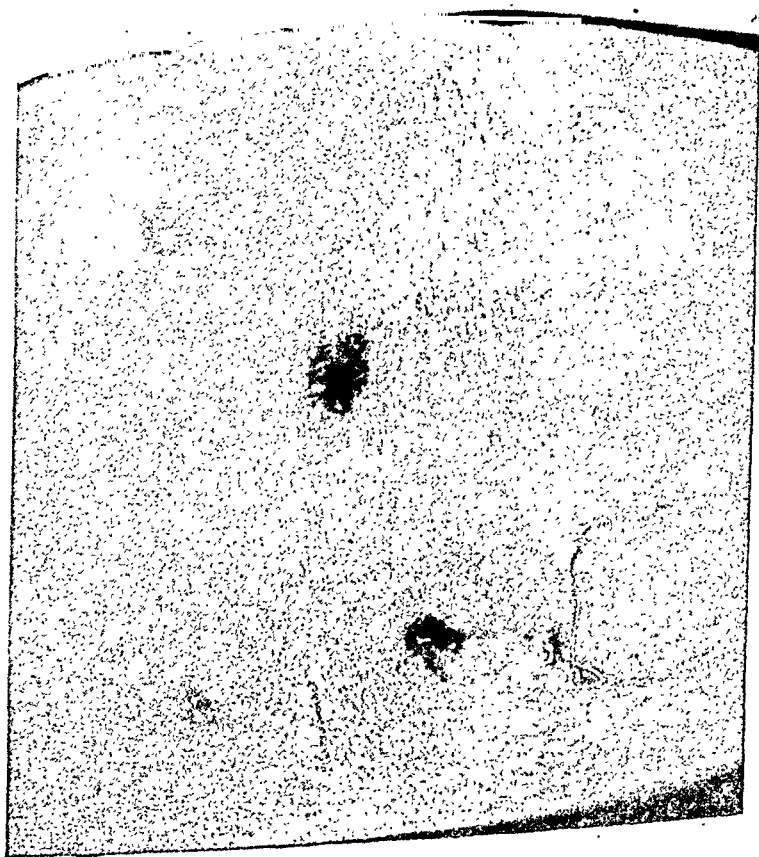


FIG. 20. Cirrhosis of the liver.* This photograph shows spiders which are forming at the site of two healing paracentesis wounds in the abdomen, indicated by the two dark marks in the center of areas of increased vascularization of the skin. The upper mark represents the site of a paracentesis performed nine days before the picture was taken; the transverse mark below it, the wound made five days later. The navel may be seen in the upper left corner of the picture, and in the lower right corner, a wound still exuding ascitic fluid, the result of a paracentesis performed only a few hours before the photograph was made.

central vessel to form the outer portion of its wall. In the central vessel the elastic lamella becomes thinner, loses its wavy character and finally disappears after breaking into delicate threads. The muscle fibers of the outer media retain the circular direction present in the afferent artery." It was emphasized that this structure was not a glomus body because there was no arteriovenous shunt. The lumen became progressively narrower; the many branches finally emptied into capillaries. Proximal branches retained a single layer of endothelium and

* This case has been reported as Case 3 in a review of palmar erythema (17).

inner cellular layer but lacked the external layer of muscle. They suggested that this structure was the result of metaplasia of already existing arteries in the skin, a process which caused them to resemble glomus vessels, and of their subsequent hyperplasia.

Walsh and Becker (182), in their review of erythema palmare and naevus-araneus-like telangiectases, included a low-power view of a section of one of the latter lesions. They state that "the lesion, reconstructed from serial sections, seemed to consist chiefly of an arteriole branching from one of the arteries just within the subcutis. This vessel traversed a somewhat tortuous course to about the subpapillary layer of the cutis. Here it seemed to change directly into a vein of comparable size without intervening capillaries, which in turn divided into the network of smaller venules which form the gross spider-like appearance. It had a muscular wall of about normal thickness for a vessel of its size (0.25 mm.) and was accompanied by a nerve whose fibers seemed to end in the vessel wall." Despite this description they called the lesion a small arteriovenous anastomosis.

Murray and Stout (133, 175) have shown, by the tissue culture method, that the "epithelioid" cell of the glomus is derived from Zimmermann's pericyte (192), a modified smooth-muscle cell. In their photomicrographs the various stages of development may be seen in convincing detail. The almost imperceptible gradations in the glomus canal (Sucquet-Hoyer) from arterial smooth-muscle cell to "epithelioid" cell to venous smooth-muscle cell, as well as the contractile power of each of the three types, speak for an affinity of "epithelioid" cell and muscle cell.

The glomus cell has well defined characteristics which are most pronounced wherever it is most highly differentiated from the smooth muscle of artery and vein. Many gradations occur between the glomus and the muscle cell, and mixed cells with some of the histological characteristics of both may be found. The aspect of the glomus cell varies considerably, depending upon the compactness or looseness of the tissue in which it occurs. These cells are round for the most part, and have large, dark-staining nuclei in the center surrounded by a clear zone of cytoplasm which stains little or not at all. Reticulin fibers appear between adjacent cells. According to Murray and Stout (133), the usual picture of many tightly packed cells distorts the real character of the individual cell. In their study of tissue cultures of glomus cells the "epithelioid" markings changed into those typical of the pericyte of Zimmermann.

Observations

Vascular spiders were studied histologically during this investigation whenever a biopsy or autopsy specimen could be obtained. The first few lesions studied in this manner six years ago were sectioned only once or twice. A very confusing picture resulted, in part because of the distortion from its living form which occurs in the skin and its nutrient vessels when a small portion is removed from the anchorage of the surrounding tissue. The piece removed shrinks to less than half its normal size and becomes irregularly puckered and wrinkled.

The vessels disappear from sight as soon as the incision is made for a biopsy. This source of difficulty has been partly obviated by fastening the specimen to cork with pins so that it retains its proper size, but some distortion persists. It is well to remember Knisely's (107) admonition regarding the size of small vessels: "...For after the abuse which the tissue undergoes in death and fixation, shrinking and swelling in various reagents, a capillary's diameter has no known or knowable relationship to the size or sizes that it had in life."

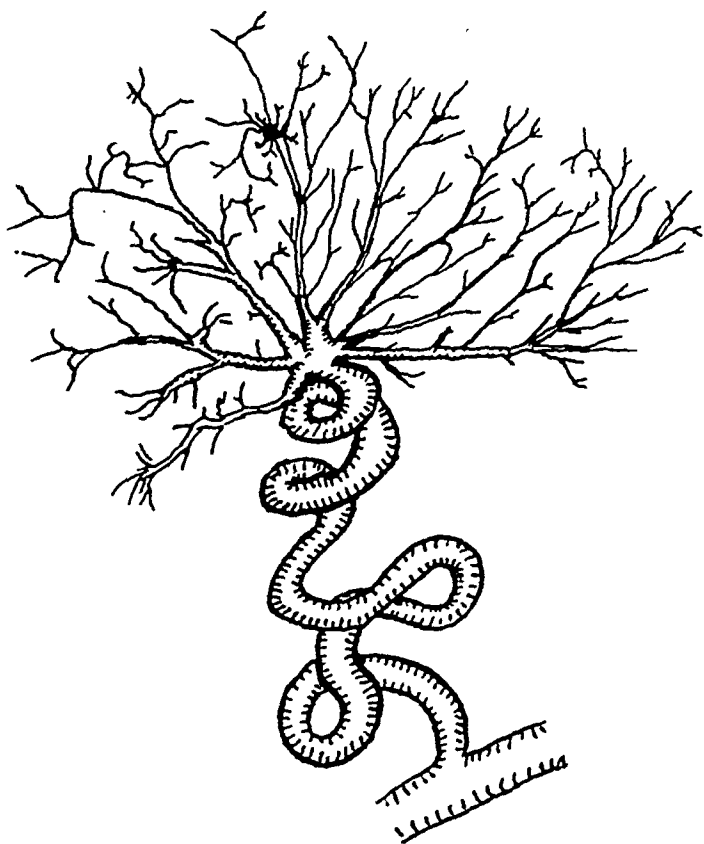


FIG. 21. Schematic drawing of a vascular spider, showing the coiled artery; the central boss; the branches, some of which end in secondary knobs; the anastomoses between branches, and other details. The coiled artery is disproportionately large.

Attempts to obtain sections in which the original relationships were not destroyed have not succeeded. Repeated efforts at *intra vitam* injection *in situ* have resulted in profuse spurting hemorrhages, whether the cannula was directed toward the central boss, the stem artery, or one of the larger radicles. If some scheme can be devised which will enable the injection and fixation of the intact vessels and subsequent clearing of the specimen, or dissection, it will reveal the more complex aspects of its structure in their normal relations.

Serial sections of 28 individual lesions from 11 subjects with hepatic disease have been examined.¹⁴ They were taken from the skin of the neck, shoulder,

¹⁴ This work was done in collaboration with Dr. Seaton Sailer. Unfortunately the entire collection of slides has been mislaid, and the following section is written from preliminary studies and notes.

chest, back, upper and lower arm. An extension of this phase of the work to include spiders in pregnancy, deficiency diseases, and in normal persons is fundamental to further understanding of the subject. The ensuing discussion is based on observations limited to spiders from persons with hepatic disease. Careful inspection of the vascular spider during life, and subsequent study of the same lesion cut in serial section have elucidated some of the questions not answered by either method when employed alone.

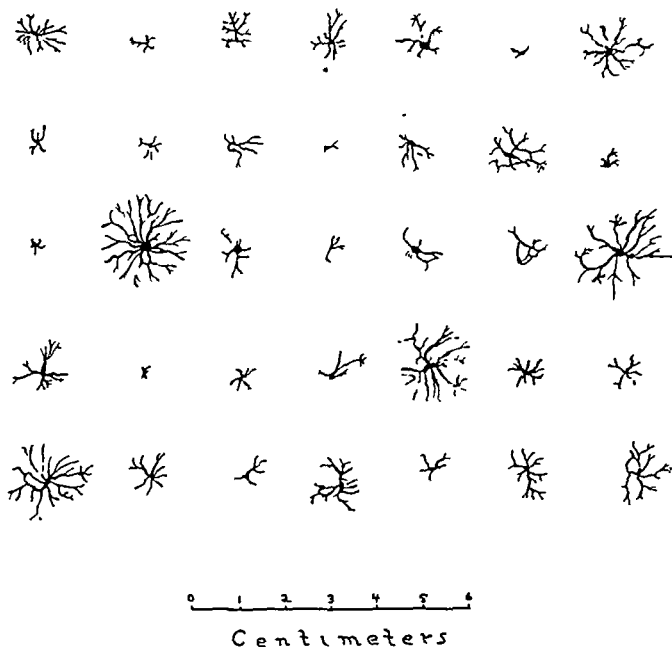


FIG. 22. Scale drawings of actual lesions showing the variety of pattern and size

In gross structure the spider may be compared to a branching coral formation whose fronds radiate in a narrow plane parallel to and just below the skin and perpendicular to the main axis of the gnarled or coiled stem. Some lesions call to mind the stump of an uprooted tree. A few spiders with the central eminence elevated reproduce in miniature the *Caput Medusae*. A prominent part of the structure, the coiled and tortuous main stem artery, has not received careful study, although it has been noted by others (145, 147, 188). In some instances when the superficial vessels have been scanty, the upper end of this vessel examined during life with retrograde illumination resembled in shape the coiled arteries of the endometrium (10, 11, 12, 105, 123, 124). In the case of

7

... is incapable that the deformity has resulted ... between two relatively fixed points.

... the spider schematically. Many ... the central punctum or body. The latter may ... the side surface, but large lesions almost invariably ... a rounded knob or boss. The structure of the ... because the irregular contractions of ... produce bizarre deformities when the vessels are ... appears to be an aneurysmal dilatation in some cases, ... branching vessels in others.

... and decrease in size as they branch in ... (Figs. 21 and 22). Macroscopic anastomoses ... the larger or smaller vessels but they are uncommon. ... twenty times, anastomoses not otherwise noticed may ... the legs may be gracile or knobby, straight or crooked, ... It is usual for different forms to exist in a single lesion. ... in the course taken by a single radicle as it dips deeper below ... the caliber of the vessel undergoes attenuation, suggesting ... of the muscle wall or local sparsity of muscle fibers. Bul- ... and breaking also occur. When the entire area covered by the ... and studied with a dissecting microscope or with a slit ... one finds connecting legs leading to small satellites which ... the characteristics of the larger lesion on a reduced scale (Figs. ...).

Histology

The most typical spiders consist of a coiled artery with many glomus cells ... This artery decreases in ... as it gives off branches of similar ... whose walls rapidly ... the lumen may ... of spider differs ... of so large an ... wide dilata-

Type I. In only three of our ... out ... did we fail to find ... cells. ... the same in these sp ... as in ... the first class of ... bed ... Type II. Spider ... the gl ... found might be di ... seve ... rarity of these cell ... of the ... corresponded exactly. ... repr ... striking differences co ... main ... or glomus cells.

Serial sections of the ... high ... and glomus cells were ... ti-

next would come a sudden or gradual thinning of these cells until the artery did not differ from a normal artery in such a region; then, following a course towards the surface of the skin, the wall of the vessel would continue substantially the same on one side but on the other a great piling-up of glomus cells would appear. This was not the result of cutting at an angle for it occurred on either the acute or obtuse side of a kink. Sometimes in the same main-stem artery, a second cuff of widening in the vessel wall was seen, with the same packing of glomus cells. This gave the impression of a gross beading of the



FIG. 23. Section of vessels from a vascular spider near the surface of the skin. Near the center, just below the surface, is a dilated thin-walled vessel, a typical leg or radicle. Much smaller vessels may be seen in this level, to the left. In the lower center appear two large thin-walled vessels which branched off from the narrow, thicker artery (seen in longitudinal section) pointing toward the lower left corner, where it has been cut transversely. Magnification $\times 160$.

external aspect of the vessel but the lumen remained about the same in diameter. Some of the beads were eccentric, as though strung far from their true center.

In most instances the body or boss seemed to have been deformed by the contractile forces which acted without counter-pull after the specimen was removed and before it was fixed. Many contained the same type of cells which occurred in the main arterial trunk. A few had very thin walls without muscle or pericyte cells. Irregularly disposed branches at their proximal attachment usually possessed the same variety of wall as the central punctum. The thick irregular heaping-up of compact pericytes was found in most cases.

Legs of the spider repeated the changing patterns found in the main coiled artery. Near the site of their emergence they usually had thick walls with smooth-muscle cells and pericytes, sometimes commingled, sometimes segre-

gated. As the periphery was approached there was a well marked tendency for the wall to lose both muscle and pericyte. At the point of branching or of a sharp angulation, however, there was more often than not an accumulation of pericytes. Most characteristic of these vessels was their relatively large size and very thin wall, not more than two cells thick (Figs. 23, 24, and 25). These vessels sometimes arose directly from the central eminence with the thin coat they retained throughout their course. In others there was a gradual transformation from thick-walled artery to thin-walled blood vessel. Some radicles showed the beading phenomenon with regular or eccentric bulges of the vascular coat caused by congregations of pericytes. Just beneath the skin they were uniformly thin-walled and distended with blood (Figs. 23 and 24).

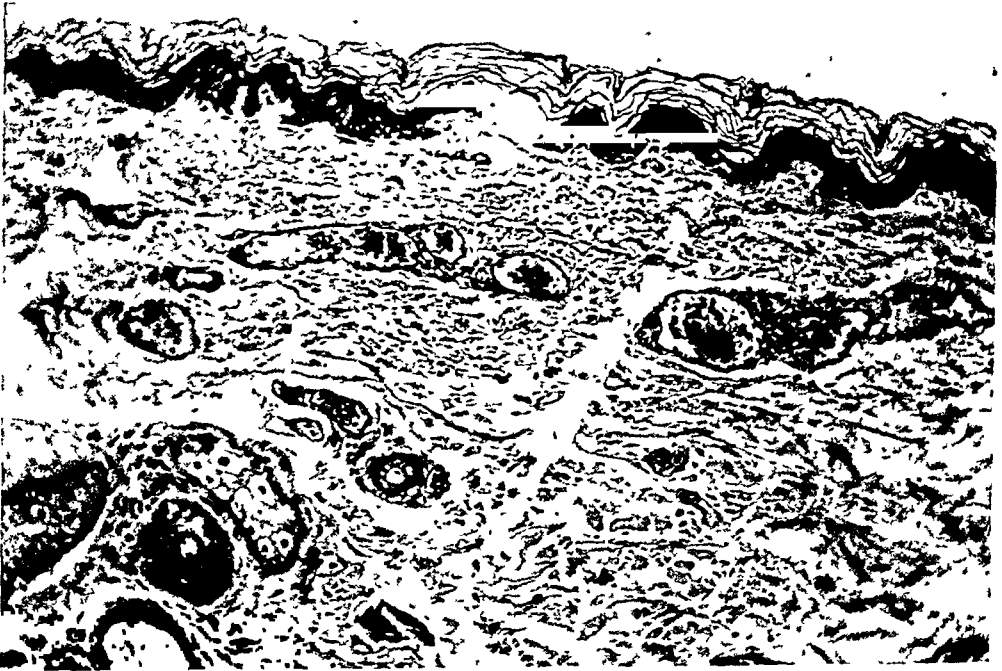


FIG. 24. Section showing the distribution of the thin-walled vessels of various diameters near the surface. This indicates the frequency with which branches from the radicles radiate from the central vessel. Magnification $\times 160$.

It should be emphasized that the vascular spider is not an arteriovenous anastomosis in any ordinary sense. The blood flowing rapidly, under high pressure, comes up through the spiral artery to the punctum, whence it flows peripherally through the legs or radicles, which may look like veins or arteries but nonetheless carry arterial blood. From this point the vessels decrease in caliber, their walls become attenuated, and they pass into a capillary bed which is spread throughout the area supplied by the main vessel. Finally, capillaries have a peripheral confluence in small veins tributary to the collecting veins which carry the venous blood back into larger channels. This promiscuous association of veins and arteries is unique. It has given rise to confusion and ambiguity because in the past the arterial spider normally has been categorized as artery or vein, depending on the dominant structure included in a random section.

A more detailed consideration of the histopathology and living architecture is needed in order to determine whether some of the gatherings of pericytes in the regular and lopsided collections we have seen are artifact or the result of contraction caused when the specimen is removed from its moorings. Observations made so far point to the conclusion that the vascular spider constitutes an enlargement and overgrowth of the nutrient artery of the cone-shaped region of the skin described by Renault. Whether the glomus cells, the pericytes of Zimmermann, proliferate from small rests scattered throughout the blood vessels generally, or are the result of metaplastic forces is obscure. The true glomus



FIG 25 This section cut near the terminus of the coiled artery where it breaks up into "veins," shows both types of vessels in close proximity. From study of adjoining sections it became evident that changes had taken place in the walls of a single vessel, with thick and thin segments alternating irregularly. This picture gives a good indication of the architectural disarray resulting from the processes of fixation and cutting of the material. Magnification $\times 160$

has a distribution very different from the favorite locations of the vascular spider (13, 87, 152, 177).

THE DIFFERENTIATION OF THE VASCULAR SPIDER FROM OSLER'S DISEASE (HEREDITARY HEMORRHAGIC TELANGIECTASIA)

Babington (9) in 1865 was probably the first to describe a case of hemorrhagic telangiectasia of the hereditary type; Rendu (155) described a family with the disease, which he designated by the term pseudohemophilia; and Chauffard (41) and Kopp (109) reported cases. Sir William Osler was the first to establish the true character of the disease in his classical reports (135, 136, 137). He brought it out of the group of mysterious hemorrhagic disorders. Parkes Weber (139, 140, 141, 144, 146) elaborated upon the description, noted the differences between this condition and hemophilia, the absence of sex-linked

transmission, and the tendency for epistaxis to antedate the appearance of telangiectases. Hanes (90) discussed the histology and stressed the conjunctival lesions, involvement of the nail beds, the atypical dilated vessels scattered in the skin, and the fading of the lesions after hemorrhage. Fitzhugh (68, 69) and others (31, 130) have reported cases with complicating hepatic disorders. The disease has been reviewed extensively and exhaustively (3, 45, 46, 51, 54, 61, 63, 82, 84, 88, 90).

At first view it may seem redundant to include a discussion of this well documented disease in this review. But in spite of the many descriptions of the characteristic telangiectasis, there is recurring evidence that it is mistaken for the vascular spider, and vice versa. A superficial similarity between the two conditions has been noted by writers who have supposed that they were but minor variants of one disease (31, 51, 68, 69, 130, 188). The occurrence of splenomegaly and hepatomegaly in a few cases of Osler's disease has doubtless encouraged the mix-up. However it may have arisen, there is nowhere a clear-cut presentation of the typical features of Osler's disease which permits the absolute separation of ordinary examples of the two distinctive lesions.* Since this confusion may result in unfortunate errors in treatment and prognosis, and egregious mistakes in the understanding of the fundamental nature of the lesions, the differential points will be considered here in detail.

During the study of the dermal vascular spider I observed a number of families with Osler's disease¹⁵—miserable bleeders who made their perennial pilgrimages to different services of the Cincinnati General Hospital, seeking control of their ubiquitous hemorrhages. Several dozen victims of the disease have been examined at one time or another. It has not been uncommon for one of these patients to be in a bed next to a patient with vascular spiders, thus presenting an opportunity to compare the two lesions side by side.

DIFFERENTIAL DIAGNOSIS

Family History: The diagnosis of Osler's disease cannot be made unless the hemorrhagic tendency exists as an hereditary trait in the family. Although skipped generations have been reported, atavism is rare (68) and the factor for telangiectasis is dominant. It is possible that telangiectasis was not evident at the time of death in the generation supposedly free from the disease, because occasionally the diagnostic lesion may not appear until the fifth decade (13). In the case of the vascular spider a history of familial occurrence is more often absent than present. Since spiders do not hurt and rarely bleed, knowledge of their presence may merely reflect a well developed cosmetic sense. It is probable that a familial factor, at least of predisposition, exists but is not brought to the attention of the patients by the urgency of any complicating event. Whether this trait is a Mendelian dominant or recessive cannot be stated.

*Since this was put in type I have found an article by A. Schüpbach (Schweiz. Med. Wchnschr., 73, 1186-1943) which contains an excellent discussion of many points in the differential diagnosis of spiders and Osler's disease.

¹⁵ Many of these cases were collected by Dr. Richard Stevens, now of Huntington, West Virginia.

Hemorrhagic Tendency The tendency to bleed is so much a part of Osler's disease that it has become affixed to the Latin title. Some clinicians have gone so far as to insist upon it as a *sine qua non* of diagnosis. Occasionally one can make the diagnosis in a person whose family is affected and who has the lesions, before he has bled from them. Rarely, however, do the lesions appear before the tendency to bleed is well established. We have seen cases in which the trait was detected in a child before it was noted in the parent, who later developed the complete syndrome. It can scarcely be argued that the parent did not have the disease until he bled. From the telangiectatic lesion in Osler's disease arterial blood may spurt forth, and very rarely a pulsating



FIG 26 In the upper portion of this photograph a leg, cut along its long axis, may be seen emerging from the coiled artery. The latter is sectioned in several directions at different places, and its tortuous character is evident. Smaller branches of different types occur in several places. Magnification $\times 160$.

jet may be seen. Spontaneous pulsation is hardly ever felt in the lesion. Repeated bleeding and exsanguination belong to this syndrome, rather than to that of the vascular spider. In the case of the acquired vascular spider, particularly the dermal lesion, bleeding is an unusual complication, although hemorrhage from a spider may be copious. When disease of the liver is severe, the prothrombin deficit may be responsible for bleeding. On the other hand spiders bleed, upon occasion, when the prothrombin level is not low (13). When bleeding occurs, bright red arterial blood spurts from the lesion. Trauma can be blamed for starting it in most instances, for example, a person may believe that he is dealing with a pimple, may squeeze the top off and be startled by the pulsating jet of blood he releases. I have not seen bleeding in a spider acquired during pregnancy but some of the women themselves have re-

Among 267 persons with spiders, bleeding has occurred from the skin in 18, but "false hematemesis" (i.e. without esophageal varices) was never established with certainty in more than 50 cases of gastroenteric hemorrhage. Mucosal bleeding is exemplified by Case 5. A positive history of nose bleed was obtained in 15% of the cases in which the patient was questioned specifically regarding it.

Age at Onset: In Osler's disease one is struck with the frequently echoed story of nosebleeds as a child, a period free from hemorrhage, and the recurrence of often repeated hemorrhage at the time the tell-tale telangiectases become prominent, usually in the third decade. The lesions do not go away spontaneously, and unless a profound anemia causes them to fade they can always be found. The vascular spider of chronic hepatic disease may develop before the hepatic disorder is manifested clinically. Age at onset varies with the

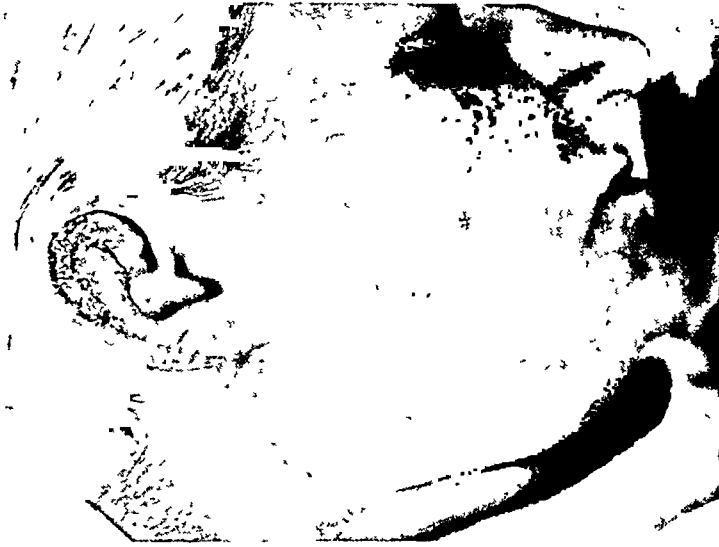


FIG. 27. Case 8. Osler's disease. This picture shows the typical lesion of Osler's disease, both in the mat form in the ear, and the papular, reddish purple, well-circumscribed lesions on the cheek, nose, eyelid and lip.

period at which cirrhosis occurs. Spiders tend to vary in size and number with the severity of the disease. Explosive bursts of spiders may erupt within 10 days,¹⁶ and they may fade rapidly, vanishing within five to six days. Ordinarily they commence as a single tiny red point which enlarges and throws out legs, which enlarge and branch. With growth, the central punctum may become elevated. Regression follows the opposite course; the legs seem to lose branches and become attenuated, while the erythematous area becomes pale. Finally the red center alone remains and it gradually fades, leaving occasionally a faint trace of brown pigment, slight dermal atrophy, or at times nothing to indicate its former existence. In normal persons there is a tendency, perhaps dependent on the powers of observation, for spiders to be noted around the time of late adolescence. They occur in infants and children, but frequently those which have appeared in the very young disappear or diminish in size after two or three years. Whether they reappear later is not known.

¹⁶ In at least two patients new spiders appeared literally overnight.

Gross Morphology: It is possible to differentiate vascular spiders from the telangiectatic lesion of Osler's disease by clinical characteristics alone. In Osler's disease the typical cutaneous lesion is punctiform. It is a spot, sometimes elevated, sometimes flat, which has very sharp margins separating it from the normal skin surrounding it. There may be a single vessel connected with



FIG. 28. Additional case of Osler's disease. The small, elevated spots characteristic of hereditary hemorrhagic telangiectasia are displayed prominently over the entire face, and show up well on the tongue.

the punctum. Sometimes there are several branches, and then the lesion may assume much the appearance of the acquired vascular spider; but in such cases there are always other spots or papules sharply isolated, with no legs attached. Solid, cyanotic looking, nodular forms occur. The uncommon spider-like lesion in Osler's disease appears to indicate that the vascular weakness happened to involve one of Renault's terminal arteries and its arteriolar ramifications in the skin, accentuating the normally invisible structure to the point where it can be seen.

Histopathology: The basic pathological alteration in Osler's disease is a thinning of the walls of the vessel, an attenuation of the muscle coat which leads to a bulging or ballooning of the wall, the defect often being extensive enough to give rise to tortuous, coiled masses of aneurysmal vessels (Fig. 23). The vascular spider has been described above (See Histology).

Besides the architectural differences, it is usual to find some differences in the *color* of the lesions. The arterial spider has the bright red color of well oxygenated blood, which suffuses the whole region encompassed by the many



FIG. 29. Additional case of Osler's disease. The hands of the patient in Figure 28. The lesions here are flat and a few are covered with white atrophic skin where bleeding has occurred in the past. Small telangiectases may be seen on the wrists. Comparison of these lesions with the vascular spiders shown in Figures 6-20 will illustrate the differences in the characteristic lesions of the two diseases.

branching legs. The telangiectasis of Osler's disease has a purplish red cast, although its arterial nature is well known.

Pressure on a vascular spider produces complete blanching. When the pressure is released the centrifugal blood flow fills the larger branches and immediately suffuses the region rendered pale by compression. Pressure on the lesion of Osler's disease may cause some fading but it is rarely complete, nor is color restored as rapidly as in the vascular spider. This may be due to the circuitous course of the main vessel involved. The pressure needed to blanch the telangiectasis, as determined by the capsule studies, is in the same range as that required to obliterate the vessels of the vascular spider. The

lesion in Osler's disease fades more slowly and less completely, and at times small islands remain even when the pressure approaches that in the large arteries. It is as though a kink had occurred, with vascular strangulation.

Pulsation is rarely felt in the telangiectases of Osler's disease.

In average size the vascular spider is many times larger than the lesion in Osler's disease (See Photographs). The central punctum in both conditions is often of the same size, 1-3 mm.

Skin temperature over a large vascular spider is always higher than that of the adjoining skin. No difference has been detected between the involved and the normal skin in Osler's disease, but the electrode used was more than a centimeter in diameter, and a smaller one might have revealed differences (13).

Distribution: The typical distribution of cutaneous vascular spiders has been noted (Figs. 1-5). The sites of predilection coincide with the flush area. Cervical vessels, costal fringes, and small telangiectatic meshes follow the same scheme in respect to their distribution. The mucosa of the mouth, tongue, pharynx, and rectum may be affected. Among some thousands of lesions I have seen fewer than 20 typical vascular spiders situated below the level of the umbilicus; but they may occur even on the toes. In Osler's disease the mucous membranes frequently present more lesions than the skin, but I have seen no case in which the abnormal vessels could not be found in both. They may appear in any part of the skin, and although more occur in the upper portions of the body, they may usually be found on the legs and feet as well. Mucosal telangiectases are almost always visible in Kiesselbach's area on the nasal septum, and on the tip and dorsum of the tongue (Fig. 28). Hemorrhages from the stomach, bowel, lung, meninges, brain, kidney, bladder, and liver attest their universal range. In the skin they differ from the vascular spider by their frequency on the palmar surface of the hands and fingers, their usual occurrence in the nail bed, the lips and the ears. This suggests that the lesion in Osler's disease follows the same pattern of distribution as the glomus body or arteriovenous anastomosis in the skin.

Skin color: Since most victims of full-blown Osler's disease have had repeated hemorrhages, the pale sallow color of chronic anemia may be pronounced. In patients with vascular spiders, the skin may be of normal color, or jaundiced, or may indeed show the same evidence of anemia.

After severe hemorrhage the lesions in both conditions may fade completely out of sight, returning to view with restoration of the blood. The emergence of diagnostic lesions may come as a surprise following transfusion for hemorrhage, in patients admitted to the wards in shock.

After death both types of lesions fade, as a result of the contraction of the vessel wall. It is more often possible to see the lesion of Osler's disease, in which the fading may be incomplete, than the vascular spider, which is only rarely seen as a ghost lesion 24 hours after death.

Hepatomegaly and *splenomegaly* have been encountered with sufficient frequency in Osler's disease to obscure the very definite differential points enumerated above. They have been specifically noted in not more than 2% of all

the cases reported, however. Neither of these signs has been detected in the cases of Osler's disease which we have observed. Until more evidence is brought forth it seems wiser to look upon hepatomegaly and splenomegaly as coincidental rather than intrinsic findings. Such concurrence is likely since it would be astonishing if Osler's disease conferred an immunity to hepatic disorders. Hemorrhage into the liver or spleen might possibly account for the instances of enlargement reported.

The various factors on which a differential diagnosis may be based are summarized in Table 5. An illustrative case report follows.

Case 8 (Osler's disease). 75312 J. B., a 40-year-old white married woman, a housewife, was admitted to the Nose and Throat Service of the Cincinnati General Hospital on November 17, 1941, following profuse epistaxis. She had

TABLE 5
Percentage distribution of spiders in various conditions

	HEPATIC DISEASE	PREGNANCY	DEFICIENCY DISEASES			NORMALS
			Age 0-10	10-20	20 and over	
Face.....	10.3	12.9	22	16	41	29
Neck.....	12.5	9.3	5	8	21	34
Shoulders.....	17.5	4.3	3	5	6	2*
Arms.....	21.3	32.1	17	23	17	14
Hands and fingers.....	2.3	14.5	46	43	12	4
Chest and back.....	35.6	26.7*	6	5	3	17*
Miscellaneous.....	0.5	0.2	0	0	0	0

* Not invariably examined.

It should be remembered that the density of vascular spiders can not be judged properly from these percentages because of the lack of similarity in the surface areas of the regions compared. For a comparison of the densities, see Figures 1-5.

had several previous admissions and had made numerous visits to the emergency ward and clinics for similar attacks.

Family History: The first known bleeder in the family was the maternal grandmother, who was born in Ireland in 1853, and came to America as a young woman. She had nose bleeds and other hemorrhages repeatedly and died in 1906 following an exsanguinating hemorrhage. The patient's mother, one of the two daughters who lived to maturity, had the same difficulty. She was born in Cincinnati in 1878 and died in 1929, following a hemorrhage. Of the nine living siblings (there had been 10 miscarriages) in the patient's generation, all but two had the bleeding trait, and the patient's only living son, a 10-year-old boy, although showing no telangiectases had frequent epistaxis. The details of the family tree may be found in the accompanying chart (Table 6).

Past History: The first bleeding occurred at the age of 17, five years after the menarche. It took the form chiefly of severe nosebleeds, which at times caused such weakness that the patient went to bed for a day or two. They occurred as often as twice a week, although there were periods lasting as long as

several months when she was relatively free from these attacks. Usually no precipitating factor was known. During her twenty-ninth year many red spots appeared on her face, ears, tongue, and the skin of her arms, chest, and legs. At the same time she noticed an extremely severe monthly epistaxis coterminous with menstruation. She was married at the age of 21 but did not become pregnant for 8 years. A full-term child was born dead. Delivery was attended by a very profuse nosebleed. A second child was born two years later and has been healthy except for nosebleeds.

TABLE 6

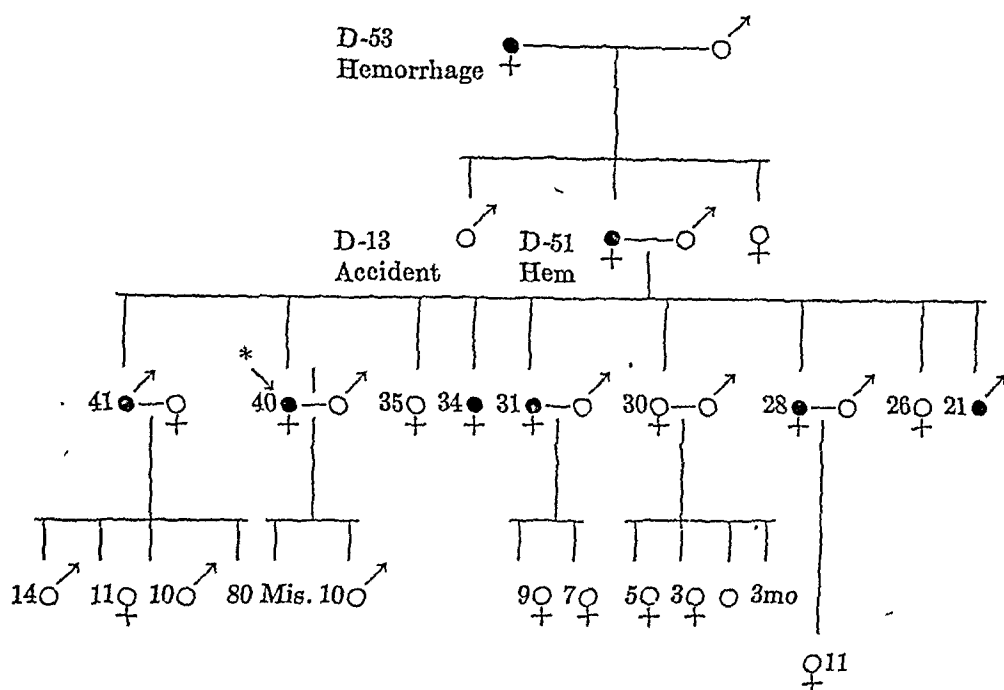
	OSLER'S DISEASE	ARTERIAL SPIDERS			
		Liver disease	Pregnancy	Normals	Deficiency disease
Familial history	+	±	?	Often +	Often +
Hemorrhage from lesions	+	Rare	Several instances in this series. Not cited in literature.	Rare	Rare
Age at appearance of lesions	In most cases, 20-30 years	During disease; usually at time of relapse or exacerbation	2nd-5th month	At birth and puberty	Any time
Morphology	Punctiform; more rarely, spider forms	Spider	Spider	Spider	Spider
Pressure in the vessels	Fades partially with 30-90 mm. Hg.	Periphery fades at 10-20 mm. Hg.; all but the center fades at 50-70, and disappears at 70-90			
Color	Red-purple	Bright fiery red			
Size (average)	1-3 mm.	Center 1-3 mm; area covered by radicles, 1-10 cm			
Number (average)	Hundreds	1-10 cm. 19	1-5 cm. 7	1-3 cm. 3	1-3 cm. 4
Skin temperature	No elevation detected by technique used	Elevated 1-3°C	Elevated 1-2°C	Elevated 1°C	Not tested
Distribution	Universal. Many in certain exposed mucosal surfaces and in skin	Most on face, neck, arms, and chest. Very rare below the diaphragm. Occasionally seen in mucous membranes (see charts)			
Behavior after death	Fade	Disappear	Disappear	Disappear	Disappear
Behavior after hemorrhage	Fade	Fade	Fade	Fade	Fade
Disease of liver and spleen	Infrequent	Usual	Not seen	Not seen	Possible

Examination: When first seen the patient was in shock and some bleeding still continued from the nose, which had been packed. The skin was pale, with a bronze tinge, and a faint indication of cyanosis added to the unusual color. Very few of the telangiectatic lesions were apparent until she had been given transfusions. They reappeared first in the tongue and ears, then on the cheeks and arms, and finally on the feet. None was found in the conjunctiva or the pharynx, but the nasal septum was corrugated with masses of vessels. The picture (Fig. 27) shows the appearance of the face and ear. The lesion in the

ear assumed the form of a net-like series of puncta and connecting vessels, whereas over the cheeks the sharply demarcated, slightly raised papular lesion is clearly seen.

Laboratory studies: Other than the profound microcytic hypochromic anemia, there were no abnormal findings. The bleeding, clotting and prothrombin times were normal.

TABLE 7



● — Affected persons

○ — Persons not affected to date (1942)

* — Case 8

Family Tree in Case 8 (Osler's disease)

Course: Following repeated transfusions the patient's condition improved and she was discharged. She refused cautery of the nasal vessels.

DISCUSSION

Clinical and anatomical data on the vascular spider have been presented in detail. It remains to consider certain philosophical aspects of the problem which are still shrouded in ambiguity and doubt. What is the nature of the vascular anarchy behind the spider? What influence does heredity have? Under what humoral tides do the lesions come and go? What local and regional forces cause them to congregate in clusters in the upper parts of the body, leaving the nether regions free, or sparsely sprinkled? Do they serve any purpose? Such questions serve to focus the light of inquiry upon our ignorance.

Heredity: Until we know the specific cause or causes of vascular spiders and

of their coming and going, we assign to that much abused force—heredity—a rôle in determining their erratic occurrence. Predisposition has in its favor the fact that family groups were observed among the patients classed as normal, pregnant, and those with vitamin B-complex deficiency syndromes. It was not established, however, even in the majority of all persons studied in these three classes; and was singularly inconspicuous among those with diseases of the liver. Furthermore, it is impossible to exclude some unknown environmental cause common to the families with several affected members.

It has been alleged that this hereditary tendency may be expressed in an anthropological type peculiarly susceptible to hepatic cirrhosis (43, 44, 47). The term, Chvostek's habitus, is found frequently in papers on the etiology of cirrhosis that have appeared in the continental literature. Chvostek (43, 44) wrote at length on the pathogenesis of this disease, concluding that certain families displayed an hereditary tendency which expressed itself physically in the male in hypotrichosis of the trunk, axillae and pubis, with dense hair on the brows, and a full beard. Enlargement of the pineal was said to occur, along with a small thyroid, changes in the hypophysis, and atrophy of the testes. These abnormalities may be found in some persons with cirrhosis, but certain considerations, to be discussed later, suggest that they may be a sequelae rather than forerunners of the disease, a part of it rather than a cause. The concept of an inherited tendency to hepatic disease includes the idea of an inherited susceptibility to the occurrence of vascular spiders in cirrhosis (141, 142, 144). Čičováčki (47) believed that the common constitutional cause of both cirrhosis and spiders in persons with Chvostek's habitus was a tendency on the part of the connective tissue to proliferate. He cited examples of the simultaneous occurrence of Dupuytren's contracture and cirrhosis in several members of a family. His reasons for supposing that vascular spiders are composed of connective tissue were not given. The evidence brought forward in the present paper does not refute the concept which Chvostek propounded. It does however cast doubt upon the thesis that there is a common cause for cirrhosis and vascular spiders, for we have shown that contrary to the allegations of Čičováčki, spiders occur in other forms of hepatic disease than cirrhosis, and also under other circumstances.

Humoral Causes: There is much to suggest that a humoral agent causes the vascular spider. This has been hinted by several observers who have written of spiders in pregnant women (33, 34, 71, 134, 182). In hepatic disorders no one functional derangement and no invariable clinical sign is associated with the lesion. This means either that no single cause operates, or that we have not found its measure. Since there are so many features common to the vascular spider of hepatic disease and those occurring in the other categories discussed, it may be suspected that one cause has provoked these lesions, wherever found. This speculation prompted a closer examination of endocrine factors which might be blamed. The arguments, outlined in a brief note (15), will be recapitulated here. Whatever merit they possess is based on clinical observation and analogy. They can be subjected to proof or refutation by fairly simple clinical experiment.

It would be unfortunate if the speculations themselves were allowed to coagulate into dogma before being put to extensive tests, but circumstances have overruled any immediate possibility of carrying out such tests.

Endocrine Disorders in Chronic Hepatic Disease: Paucity of general knowledge of endocrine disturbances in chronic disease of the liver appears to result from textbook inertia—the failure of anyone to bring together many scattered observations. The first episode to direct our attention to a consideration of endocrine dyscrasias in hepatic diseases was the resumption of uterine bleeding, irregularly profuse or scant, in a 53-year old woman with cirrhosis who had undergone the menopause nine years previously. There was no lesion in the uterus to account for hemorrhage. Uterine bleeding appeared at the same time that a crop of vascular spiders developed, and was repeated six weeks later following an exacerbation in the severity of the cirrhosis characterized by coma, jaundice, increasing ascites, a falling-off in certain liver functions, and a new blossoming-forth of spiders. It was suspected that prothrombin deficiency might be the cause not only of the uterine bleeding but possibly of the vascular spiders as well. A prothrombin deficit was not found, however, and administration of vitamin K did not affect the bleeding. Numerous studies have been made since that time but have given no indication that vitamin K and the liver's rôle in its metabolism are related to the vascular spider (13). Subsequently, other examples of the resumption of long inactive uterine bleeding have been observed. Whether "estrogenic" function resides in a variety of 17-ketosteroids normally inactivated or excreted by the liver is speculative. In women in whom cirrhosis has developed before the menopause, two types of reaction have been seen. Menstruation which had been regular became erratic, often with intermenstrual hemorrhage. In a few instances a diminution of menstrual flow occurred, even to the point of complete amenorrhea. Whether this was the same type of amenorrhea that occurs in other severe or prolonged illness, is uncertain. The majority of patients suffering from menstrual disturbances, however, have had increased bleeding or a resumed menstrual flow. This is compatible with the notion that the liver is incapable of carrying out its normal function of inactivating or excreting estrogens. Similar observations have been made repeatedly in the past (112, 138, 153, 161, 162).

Impotence in the male is a common symptom during the phase of cirrhosis which may be called hepatic decompensation (65, 153). In a few men, particularly Negroes, this rather than any other inconvenience has been the real reason for seeking aid from the physician (13). The problem of impotence is many-sided and errors in finding the true cause are easily committed, but in some patients with cirrhosis the correlation of its advent and departure to the waxing and waning of the clinical severity of the disease was so close as to seem significant. This does not necessarily mean that the cause of the impotence is an endocrine disturbance dependent on some hepatic failure. The same phenomenon is not rare in other diseases which undergo remissions and relapses, with the notable exception of tuberculosis. A strong argument favoring a direct endocrine cause exists in the testicular atrophy present in some impotent patients

who have had cirrhosis for a long time (13, 153). This has occurred in the absence of generalized wasting. Curiously enough, in an occasional case libido and potentia have increased during an exacerbation of the disease (13). These observations indicate a disorganization in the endocrine regulation which ordinarily keeps such functions within bounds, and warrant closer study of these phenomena by those expert in appraising a field where reticence or braggadocio may lead the unwary astray.

Alterations in secondary sex characteristics have been observed in a few cirrhotics with spiders (13). Most notable of these is a partial depilation of the body which may be so extensive that the distribution of hair in an adult male cirrhotic resembles that of a child. Eppinger noted this in 1925 (64). Hair on the chest and over the abdomen becomes sparse, and it is thin in the pudendal and axillary regions. Sometimes shaving of the beard is required less often than previously, but as a rule the beard and scalp are affected very little. A hairy chest and abdomen are rare in cirrhosis although baldness is uncommon. Three men who had themselves been aware of losing hair from the chest, belly and axillae during hepatic failure, found that when they stopped drinking alcohol and had ample meals regularly, so that the severity of the cirrhosis abated, their spiders receded and their hair returned to its erstwhile state within a period of three to six months. This was very striking. In two others the hair has come back surprisingly well although no diminution has occurred in the size or number of the vascular spiders (13).

Paisseau and Oumansky (138) described an hypophysial syndrome in cirrhosis of the liver and splenomegaly, which was characterized by hypotrichosis, altered distribution of body fat, retarded or reduced sexual development and activity. Laignel-Lavastine, Troisier and Boquien (112) further elaborated the picture and reported more or less complete hairlessness and evidence of insufficient thyroid and ovarian function in hepatic cirrhosis. *Additional disturbances along these lines were studied by de Gennes, Delarue and de Vericourt (77) in pigmentary cirrhosis. The syndrome they depicted was notable for the cardiac failure, low basal metabolism, atrophy of the thyroid, pancreas, adrenals and testicles, and hypertrophy of the prostate occurring in young males with cirrhosis. The degree of infantilism was extreme. The large flabby heart contained no more pigment, nor was the pigment distributed differently, than in patients dying of hemachromatosis without heart failure. Similar cases have been recorded (5, 6).

Gynecomastia in cirrhosis has been reported by Edmondson, Glass and Soll (57), who gave a synopsis of the European literature. They found badly disturbed metabolism of estrogens and androgens at a time when gynecomastia was well established. There was only one instance of this complication in our patients with vascular spiders, and it occurred before its significance was suspected. In two male patients with cirrhosis whom we have seen recently, one or both breasts have become painful but only slightly enlarged (Fig. 8), in much the same manner as may occur in boys at puberty.

The observations of Hench (94, 95, 96) on the ameliorating effects of jaundice

and of pregnancy upon certain forms of arthritis, effects produced perhaps by a common mechanism, also suggest a relationship between this mechanism and the etiological factor behind spiders occurring in the two conditions. This possibility, bolstered by the known influence of estrogens upon skeletal and joint tissues (56, 167, 168), may be another link in the chain of circumstantial evidence favoring a hormonal cause of spiders. The possibility that the B-complex vitamins, especially riboflavin, are important in the mechanism of the action of the hormones has been discussed by Biskind and Biskind (24-28). Their work opens a new field of study on the complex problem of inter-related vitamin and hormone functions. The possibility that the vascular spiders in subjects with vitamin B-complex deficiency states may be caused by hormonal disequilibrium resulting from perverted hepatic function engendered by this deficiency, is not established by our observations. But neither is it ruled out of court.

This assembly of isolated observations indicates that endocrine disturbances may complicate the clinical course of cirrhosis. These phenomena are relatively uncommon and have been absent from most cases explored carefully for such disorders. Nevertheless, the fact that there might be prolonged estrogenic action suggested that the possible relationship of estrogens to spiders be pursued further.

The investigation planned to test this idea was discontinued almost at the start. In two of the three persons with cirrhosis to whom estrogens were given, the spiders returned (15). Inunction of estrogens into the skin was discontinued before a thorough trial had been made, but no positive results had been detected (13). Much clinical and laboratory information indicates that the liver's action in maintaining proper levels of circulating estrogens may fail in hepatic disease. The clinical course and natural history of vascular spiders, although roughly following the relapses and remissions of cirrhosis, do not parallel any of the usually tested hepatic functions nor do they follow in the wake of such changes. It is not unreasonable to suppose that the perversion of some hepatic function is responsible for this class of vascular spider. The most probable cause, on the basis of clinical analogy, appears to be the liver's failure to keep circulating estrogens at a normal level. The occurrence of vascular spiders in pregnancy gives additional evidence to support this idea. The known influence of estrogens on the arteries of the endometrium, so brilliantly expounded by Barthelmez (10, 11) and Markee (123, 124), makes plausible a qualitatively similar action on other arteries throughout the body. The typical vascular spider of the skin, a coiled and enlarged end-artery of Renaut, may be but one manifestation of a series of related changes in the small vessels of the body generally. These may be noted in the mucous membranes, the skin of the nose, the palmar and more rarely plantar erythemas, the "paper money" skin, and engorgement and vascularization of the nasal mucous membrane. The suggestion is put forward that these phenomena are the result of prolonged action of estrogens and related 17-ketosteroids upon the small arteries throughout the body, especially those of the skin.

There are strong arguments against a humoral cause of vascular spiders. This hypothesis does not account for the uneven regional distribution and at first glance this objection appears overwhelming. No answer can be given if the view is taken that a humoral cause is the sole mechanism involved. Local factors must be brought in. In many diseases (pellagra, syphilis, the exanthemata) characteristic cutaneous lesions are evoked by humoral forces of biochemical or infectious nature coöperating with local factors which determine the position and extent of the changes in the skin. The term, *locus minoris resistentiae*, however little it offers in the way of explanation, nevertheless is the expression of a well known phenomenon. Therefore, a humoral agent might give rise to dermal changes which would follow a standard focal pattern.

Another argument against an underlying humoral cause is found in the abruptness of onset, of disappearance, or precipitous expansion or decrease in size, of a vascular spider. This is not the rule, because change in size is usually slow and easily measured, but individual spiders may literally vanish or appear over night. However, such abrupt vascular changes are not foreign to at least one condition which is regulated by hormones, namely menstruation.

The chief argument against an endocrine causation for vascular spiders lies in an event which although uncommon is observed often enough to eliminate anomalous behavior, that is, the concomitant fading of one lesion and the new appearance or enlargement of another in the same subject. I do not know how this fact, which has been observed by Patek¹⁷ also, can be reconciled with a humoral causative mechanism. It may prove to be utterly destructive of this hypothesis. If one may assume that very strong regional influences operate, perhaps erratically and not to the same extent in several parts of the body, then the speculation is permissible that the vascular anarchy is suppressed in one area by unknown local powers while humoral forces preponderate in another to produce or expand a spider. Or the reverse might be true. In this connection it is of interest that Clark and Clark have noted the puzzling concomitant appearance and disappearance of arteriovenous shunts in adjacent areas of the rabbit's ear.

If vascular spiders are caused by estrogenic substances, the latter are not necessarily of ovarian origin since the lesions occur in males, and before puberty and after the menopause, in women.

A final objection might be raised that spiders have not been noted in clinics where estrogens are administered in high dosage. The fact that they have not been noted does not necessarily indicate that they do not occur, because spiders may be overlooked unless one is on watch for them. Many patients are unaware of their presence.

Information about local causes or regional predisposition is mostly indirect, and there is more speculation than fact. The distribution of vascular spiders is unique. Why the body is affected in so uneven a fashion is not known. Since unmistakable lesions occur below the navel, even on the toes, the forces which determine localization are relative and not absolute. Whether they are

¹⁷ Letter to the author.

operative upon tissues of the small arteries in the skin, or are related to physiological variations in the tone of the vessels, cannot be answered from the data at hand.

A number of isolated observations on the rôle of injury in evoking the lesions have been made during this study. They would seem to support the thesis occasionally advanced that trauma acts as an agent in producing the spider at a particular site (25, 143, 145). In a case reported elsewhere (17) several spiders were removed for histological study. As one of the wounds was healing it was observed to be extremely vascular. When healing was complete, a new spider was found to have usurped the site of the old one, having its body exactly in the scar. Several tiny spiders formed in some of the spots where the stitch wounds had been, and at the same time other new spiders appeared elsewhere. This occurrence is a variation of a phenomenon which has come under observation several times. By making charts and taking photographs, it has been found that a single lesion may fade, disappear, and recur in its original site. The vessels in one spot must therefore possess a peculiar propensity for reacting to the causative agency. In the case just reported, the skin was subjected to the closest inspection during the interim between removal of the first spider and the appearance of the second one in the same location, but no abnormal vessels could be found. In another patient with cirrhosis a spider developed at the site of an abdominal paracentesis (See Fig. 20). A similar result has not been detected in any other case although many patients have been subjected to the same procedure. The uncommon location on the lower part of the abdomen is of interest. This patient and the one mentioned above also had palmar erythema (17).

One very observant patient, who had first acquired spiders during pregnancy, noticed that local changes were effected in a very unusual way at a time when she was not pregnant. Following donation of a pint of blood, a new crop of spiders appeared on the arm which had had a tourniquet on it for about 20 minutes. They did not arise as petechiae but were characteristic when seen three days after onset.

Other evidence of the predisposing effect of trauma is mostly indirect. Some patients believe that the lesion commenced as a small pustule. I have never seen this occur. In the literature one finds remarks on the initiation of spiders by insect bites, bee stings and minor local injury. Many attempts to produce lesions by inducing injury again and again at one spot in susceptible subjects have never met with success even though spiders appeared elsewhere. A point has been marked in the skin and enough histamine injected to produce the usual local reaction, two times a week for a month, but this met with no more success (13). Clark and Clark (48, 49) have noted the stimulating effect of inflammation on the development of arteriovenous shunts. Since vessels grow so rapidly in granulation tissue, foreign bodies or bacteria injected into the skin of susceptible subjects might provide additional information in our problem.

A note on teleology: The thought has recurred frequently that vascular spiders, palmar and plantar erythema, and related vascular changes in the skin might

have a function in temperature regulation, serving as an enhanced cooling mechanism, as does the true glomus. The structure of the vascular spider and the physiological state in palmar erythema are ideally suited to getting a large volume flow of blood to the skin surfaces. Whether purposeful or not, heat is readily lost under such circumstances. In some cirrhotics (153), in pregnant women, and in victims of chronic pulmonary disorders, spiders and palmar erythema might possibly represent an unusual response to strong or repeated stimulation to lose heat. This is not utterly fanciful because Clark and Clark (48, 49) have shown that at least for the rabbit ear, repeated exposure to unseasonable heat causes the formation of numerous arteriovenous anastomoses, which tend to disappear when the stimulus is removed. The notion of useful function in respect to spiders is mentioned merely as a speculation.

The possibility that the vascular spider, like the glomus, is in some way connected with cutaneous sensations, especially in the perception of temperature changes (79, 80, 81), has not been studied. Nothing in the present work has suggested such a function.

Suggestions for further study: Before work on the problem of vascular spiders was interrupted, a number of studies were in progress or had been outlined. Much more work needs to be done on biopsy specimens. This will depend in part on the development of a technique for obtaining the vessels with their natural relationship preserved, perhaps by injection *in situ*. There is need for serial sections and reconstruction of specimens obtained from persons in the several categories in which spiders occur. An attempt should be made to discover whether the histological structure is uniform; and the significance of lesions without glomus cells must be determined. In keeping with newer concepts of dermatology, the skin generally should be studied, because even casual inspection may reveal abnormal vessels in the skin in addition to the characteristic stellate forms. Because very great enlargement of superficial and esophageal veins in cirrhosis is common, these structures too should be examined for the glomus type of cell. Further study of inunction of estrogens and related compounds into the skin and its nutrient blood vessels should prove of interest. Similarly, the estrogens might be applied directly to the vessels of the rabbit ear by the methods perfected by Clark and Clark (48, 49). Changes in cutaneous vessels should be looked for in clinics where estrogens are used extensively. Finally, tissue culture, which has proved so valuable in the hands of Murray and Stout (133, 175), might offer a method of estimating the effects of hormones on the peculiar cell of the vascular spider.

RESUMÉ

1. A review of available medical papers on the cutaneous arterial spider indicates that it emerged as an entity from the confusion regarding telangiectases and angiomas about 75 years ago (Wilson). Its relationship to hepatic disease also became apparent at that time. Fifty years ago it was recognized as occurring in normal persons (Hutchinson, Besnier and Doyon). The association of telangiectasia with pellagra, perhaps complicated by hepatic disease, was

known 35 years ago (Majocchi), but attention has been directed to the occurrence of *spiders* in vitamin-deficiency syndromes for the first time in the present study (15, 16, 17, 18). Their significance is debatable. That spiders may be regarded definitely as a complication of essentially normal pregnancy was first perceived 30 years ago (Corbett). At various times they have been recognized in other diseases.

2. A detailed description of the spider has been presented. This sometimes evanescent alteration of the small vessels of the skin is characterized by a central point or body, branching legs or spokes, and an erythematous region encompassing these structures, often extending beyond the radius of the legs. The bright red color and increased temperature bear witness to the profusion of arterial blood brought near the surface. Blood flows centrifugally from the punctum towards the perimeter, and measurements of pressure reveal the arterial nature of the blood. This is verified by the use of infra-red photographs in which the structure, red from its content of arterial blood, is lost to view.

3. The arterial spider is frequently a peculiar manifestation of a wide-spread disturbance present in the small vessels of the skin, mucous membranes, and perhaps other portions of the body. This disturbance may also be expressed as a striking mottled erythema of the palms, and less often of the soles. In the latter regions typical spider forms are very uncommon. The external aspect of the nose is implicated in many instances. Vascular brushes, mats, and chaplets over the trunk may be associated with these lesions.

4. The structure of the spider is unique. The main vessel is an artery larger than those usually arising in the subcutis. It courses through a coiled and tortuous passage almost to the surface of the skin, where it breaks up into a multitude of branches which spread out immediately below but parallel to the surface. In its gross aspects the main vessel mimics the spiral artery of the endometrium. In addition to the pulsation, a whip action imparts a surprising impact over the small central spot, particularly when the latter is elevated above the surrounding skin. The general architecture implies that the spider is an overgrown artery of Renault. The main structure suggests hyperplasia and hypertrophy, being angiomatous in nature, while the radicles may be true telangiectases. An attempt to answer the question whether hypertrophy alone or benign neoplasia can rightly be said to constitute the evocative force behind the spider, would carry us beyond the scope of this paper.

5. Microscopic study has revealed that in most, but not all spiders associated with hepatic disorders, the artery has in its walls the glomus cell, the pericyte of Zimmermann, ancestor of the smooth-muscle cell of vein and artery. This cell is distributed in irregular profusion and sparsity in the walls of the main artery of the spider, in cuffs and eccentric beads which alternate with regions where the cells are scarce or absent. In some of the larger branches or legs this beading may be present also. In most of the branches, however, muscle cells are absent, and large vessels with thin walls sprout directly from an artery with thick walls. This merging of artery into vein by so promiscuous an anastomosis has given rise to the belief that the spider is an arteriovenous anastomo-

sis, and in the strictly literal sense this is true; or, to express it more accurately, the spider contains many arteriolar-venular anastomoses. But this significant difference exists—the branches carry arterial blood into smaller vessels which finally pass into capillaries, from which the blood is collected by veins that increase in size as the perimeter of the spider is reached. The concurrence of spiders and erythema of the palms and digits, and their precise limitation to the areas supplied with plentiful glomus bodies, furnish strong corroboration of their fundamental kinship.

6. The pattern of distribution is peculiar and characteristic, with some variations in the several groups. The face and neck are affected preponderantly, the arms and upper portions of the body less frequently, while only rarely do the lesions appear below the level of the midriff. The reason for this peculiar distribution is not known. A possible factor may be the variation of tone in the small vessels of the skin: spiders are uncommon where the vasoconstriction is strong, plentiful where it is relaxed. Thus the flush area is implicated in most instances. The fact that plantar erythema is much rarer than that of the palms also fits such an explanation. The mucous surfaces of the body have been explored too little to permit conclusions, but most of the lesions occurring in the mucosae have been found in the nose, mouth and pharynx, with few in the rectum and genitourinary tract.

7. Spiders may occur in the following classes of persons: 1) Subjects with liver disease; 2) Pregnant women; 3) Persons with deficiency disease caused by lack of the B-complex vitamins; 4) Normal persons.

8. The observations we have recorded demonstrate that the spider tends to occur as a complication of hepatic disorders when they are long and severe, but that no common sign or functional variation parallels its fluctuations, foreshadows its advent, or anticipates its regression. In pregnancy spiders usually appear anywhere from the second to the fifth month, and in most cases fade abruptly during the period of uterine involution. They appear to be directly associated with deficiency diseases only when the liver is deranged. In many instances their occurrence appears to be fortuitous. In the presumably normal persons so affected they are governed by forces which are altogether obscure.

9. The differentiation of Osler's disease (*hereditary hemorrhagic telangiectasia*) from the vascular spider has been considered in detail. The vascular aberration in Osler's disease is ubiquitous in distribution, pervading the inner reaches of the body as well as its mucous and cutaneous surfaces; it gives rise to repeated hemorrhage from trivial trauma; having once become manifest it does not regress; and it is inherited as a dominant trait. It is usual for a large number of lesions to occur in any victim of this disease. In size and shape this telangiectasis differs from the vascular spider. It is smaller, punctate, often of firm consistency, purplish in color, and only rarely is it pulsating. Although the vessels carry arterial blood, the lesion is a tangle of thin-walled, dilated, contorted vessels near the surface, and is not conspicuously warmer than adjacent skin. The photographs reveal other characteristic differences. The vascular spider, *per contra*, has a special predilection for the upper parts of the body, particularly

the blush area, but may occur in mucous surfaces; it may bleed, but this has occurred in fewer than 5% of our subjects. The rôle of heredity is not certain, but a familial tendency is sure in many instances. Spiders have a most curious faculty of changing size, of appearing and disappearing, of coming in explosive eruptions and perhaps fading away almost as precipitously. Many lesions are large, measuring in rare cases two or more inches in greatest diameter. Their shape is well described in their name.

10. The hypothesis has been advanced that a cause of this alteration in the small arteries of the skin is an increase or qualitative change in circulating estrogens or hormones of related chemical structure, a change that is normal in pregnancy, pathological in hepatic disorders in which the liver fails in its function of keeping the 17-ketosteroids in balance and at a proper level. Many clinical data support this concept. Crucial evidence is not at hand, but the problem is susceptible of experimental trial.

11. The possibility that the spider, the red palm, and related erythemas are structures designed to enhance heat loss has been mentioned.

12. The questions this study leaves unanswered indicate that investigation of the vascular spider is a field which could be worked with profit.

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THE CHEMICAL SEPARATION AND THE CLINICAL APPRAISAL OF THE COMPONENTS OF THE BLOOD

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PASSANO AWARD ADDRESS delivered in Baltimore, Maryland, May 16, 1945

The chemical properties of the proteins and lipids of the blood, as of other tissues, are only beginning to be apprehended. The physiological and immunological functions of the tissues depend upon the molecular architecture of these natural substances. Insight into their properties is yielding on the one hand a new morphology, on the other a new physiology, immunology and pharmacology.

An approach to clinical medicine based on an understanding of the functions of the body at the molecular level may also be anticipated. Insofar as the functions of each protein, lipid or carbohydrate component of a tissue are understood, a rational therapy to repair deficiency of this component may be envisioned. The fundamental knowledge of the body and its tissues at the level of the interacting molecules and ions upon which its structure and function depend can, it is true, be acquired but slowly. In these terms, however, an understanding may be sought of organization in health and of the disorganization which is disease.

Are we developing medical investigators to approach their problems with this training or with this insight? We recognize the chemical nature of biological phenomena and we study the influence on bodily processes of a large number of chemical substances. Does it suffice, however, for the chemist to prepare the molecules in which he is interested, and for the clinician to attempt to discover by trial and error their behavior in the body and their possible value in therapy? The pharmacopoeia contains many substances which were discovered where time and space separated the chemist, with his insight into molecular structure, from the clinician, with his insight into the range of phenomena associated with disease. If empiricism is to give way to theory, however, we must discover a pattern for research in which different disciplines contribute to the development of an integrated understanding.

The achievements which you are recognizing and honoring were born of an attempt to develop such a pattern. Asked in 1940 whether we would undertake a study of blood substitutes for the National Research Council and agreeing that the development of such substances was in essence a chemical problem, we replied that the rapid progress demanded by the threat of war could be achieved only by intimate day-by-day collaboration of the chemist and the histologist, the immunologist, the internist and the surgeon. For almost five years a group of men have labored together¹ in the hope of furthering a systematic understanding of

development has included G. Scatchard, J. T.

W. L. Hughes, Jr., Major R. M. Ferry, D. J.

Alford, D. A. Richert, A. Brown, A. H. Sparrow, M. Melin, J. N. Ashworth, A. C. Batchelder, M. H. Blanchard, J. W. Cameron, H. T. Gordon, P. M. Gross, Jr., S. G. Miller,

the chemistry and functions of the blood proteins as a rational basis for blood therapy.

In honoring me you are honoring this group of brilliant collaborators. The results that have been achieved, and the products that have been made available to the Armed Forces are the outcome of the merging of physical and chemical with histological, immunological and clinical thinking. The interplay of the ideas of my collaborators, trained in different disciplines, has yielded a series of products from the blood collected by the American Red Cross. Certain of these—serum albumin, the gamma globulins, the blood grouping globulins, thrombin and fibrin foam—have been prepared in large amounts under Navy contracts. Others, developed under contracts with the Committee on Medical Research of the Office of Scientific Research and Development, for which chemical studies are complete, as in the case of fibrin film, can now be made available to the Armed Forces. Should any of these, or other derivatives of therapeutic value, developed from the blood contributed by the American people to the war effort, become available in excess of military needs, it is to be hoped that the American Red Cross may arrange—as they have in the case of the gamma globulins—for their return to the people in the interest of the national health.

P. R. Morrison, Lt. H. L. Taylor, H. (S.), U.S.N.R., Lt. E. J. Klein, H.C., U.S.N., M. M. Hasson, M. H. Smith, C. G. Gordon, M. J. E. Budka, M. Y. Clark, M. E. Collier, J. Weeks, R. N. Kelty, L. H. Larsen, and G. N. Thurber.

Our clinically trained colleagues have included the late Soma Weiss, C. A. Janeway, S. H. Armstrong, Jr., O. T. Bailey, F. D. Ingraham, Lt. Comdr. S. T. Gibson, M.C., U.S.N.R., Lt. Comdr. L. M. Woodruff, M.C., U.S.N.R., Lt. E. A. Bering, Jr., M.C., U.S.N.R., Lt. J. T. Heyl, M.C., U.S.N.R., C. v. Z. Hawn; C. W. Ordman, W. Berenberg, H. Schlesinger; and the immunologists, J. F. Enders, W. C. Boyd, Lt. L. Pillemer, Sn.C., A.U.S., J. C. Sullivan and their assistants.

In addition, we have been greatly aided by the collaboration of the Bureau of Medicine and Surgery of the United States Navy, by the American Red Cross, by members of the Subcommittees on Proteins (Chemistry), on Blood Substitutes and Neurosurgery (Medicine) of the National Research Council, by many colleagues in other departments of Harvard University, among them, O. Kraye, L. K. Diamond, G. W. Thorn, J. G. Gibson, 2d, F. D. Moore, F. H. L. Taylor, C. B. Favour, and in other institutions, notably by H. B. Vickery of the Connecticut Agricultural Experiment Station, A. R. Dochez of the Committee on Medical Research of the Office of Scientific Research and Development; E. S. A. Robinson and G. Edsall of the Massachusetts Antitoxin and Vaccine Laboratory, Capt. L. R. Newhouser, M.C., U.S.N. of the National Naval Medical Center, Lt. Col. D. B. Kendrick, Jr., U.S.A. of the Army Medical School, J. M. Luck of Leland Stanford University, and J. W. Williams of the University of Wisconsin, J. Stokes, Jr., of the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and other Epidemic Diseases of the Army, D. D. Rutstein of the Department of Health of the City of New York, D. W. Richards, Jr., of the College of Physicians and Surgeons, Columbia University, and Bellevue Hospital, E. A. Stead, Jr., of Emory University, O. H. Wangensteen of the University of Minnesota, and the groups associated with them.

Our own work in recent years, as well as that of many of our collaborators in other institutions has been carried out under contract recommended by the Committee on Medical Research to the Office of Scientific Research and Development.

RED BLOOD CELLS

Blood is the fluid tissue of the body which is in equilibrium with all other tissues. Into it are poured the hormones which regulate many bodily functions. Even the most copious components of the blood, the red blood corpuscles concerned with respiration and the albumin largely responsible for maintaining the equilibrium in water and electrolytes between blood and the tissues, are formed in other tissues of the body. In normal man their life in the blood stream, as that of many other natural protein and lipid components, is limited at most to a matter of months. When they are lost from the blood stream replacement therapy should take into account the rate of their regeneration, in order that their concentration in the blood and as reserves in the tissues approach the normal level; in order that normal concentrations of blood components be re-established and not deranged as they may be by introduction into the body of foreign substances.

When there has been severe loss of blood or when major operations are to be performed in which severe blood loss is anticipated, it is necessary to supply the red blood cells present in whole blood in sufficient amount and to restore the rate of circulation of the blood so that adequate amounts of oxygen are supplied to the tissues. The oxygen is transported by the hemoglobin concentrated within the red cell. Whereas the protein content of the surrounding plasma is but 7 per cent, the hemoglobin content of the red cell is over 30 per cent. Is the function of the red cell to concentrate the oxygen-bearing protein to this extent without deranging the equilibrium in water and electrolytes between blood and the tissues?

SERUM ALBUMIN

Albumin is the protein in plasma largely responsible for maintaining the volume of the blood. The force which holds water in the blood stream and which is exerted by the molecules to which the blood vessels are impermeable is colloid osmotic pressure. The fibrinogen, which is the structural element of the blood clot, represents but 4 per cent of the protein, but exerts less than 1 per cent of the colloid osmotic pressure of the plasma. The gamma globulins which are the bearers of many of the immune properties of the blood represent but 11 per cent of the protein, but exert only 5 per cent of the colloid osmotic pressure. The lipoproteins which represent over 20 per cent of the protein exert approximately 7 per cent. The lipid-free alpha and beta globulins and the albumin are responsible for over 85 per cent of the osmotic pressure of the plasma. These components have now been prepared in a state in which they can be safely injected in man. The chemical nature and the specific functions of these alpha and beta globulins are now being investigated so as to determine their value in therapy. The albumin, which represents over 50 per cent and is now the best known of the plasma proteins, has proven of value in the treatment of shock, hypoproteinemia and edema.

Albumin is the most soluble of the proteins in plasma. It is readily prepared

as a concentrated 25 per cent solution which can safely be injected with great rapidity. Large amounts of this blood derivative have been prepared under Navy contract and used in the clinic and in the field. Albumin is the most symmetrical of the plasma proteins. It therefore exerts a smaller effect in increasing the viscosity of the blood than other plasma proteins. As a result it draws water into the blood stream and increases the circulating volume of the blood with the least burden to the heart.

Albumin can be prepared with a low sodium content in the interest of increasing its efficiency as a diuretic agent. It is the most stable of the plasma proteins, can be heated in the presence of certain salts to 60° or 64°C. for ten hours in the final containers and, sterilized in this way, dispensed without a mercurial preservative.

GAMMA GLOBULIN

When albumin is injected into the blood in excess of need it is not lost by the body but finds its way to the tissues where it is presumably stored as a source of energy or new protein. The equilibrium between blood and tissues in the case of the gamma globulins, which are responsible for many of the immune properties of the body, is at least as important. Were the antibodies of the blood stream completely responsible for the immunity of the body we would expect normal pooled plasma to protect against all diseases to which a society acquires life-long immunity. Such is not the case. However, the antibodies to certain diseases are present in normal human plasma in sufficient amount to render effective protection by passive immunization with the concentrated gamma globulin being made available to the Armed Forces and, through the American Red Cross, to public health agencies. Among these diseases, as has been beautifully demonstrated by Stokes and others, are measles and infectious hepatitis.

In most diseases where the value of convalescent serum has been demonstrated, the effectiveness of the concentrated normal gamma globulins may be anticipated. This follows since the level of the antibodies in convalescent serum is rarely concentrated over that in normal pooled plasma by a factor greater than the twenty-five fold concentration achieved by our chemical fractionation process. If this fractionation process is employed in concentrating the increased amount of antibodies in the blood stream, either during convalescence or as a result of chemical or immunological stimulation, far higher antibody titers can be achieved. Such concentrated convalescent and hyperimmune gamma globulins are now being investigated.

Is the immunity in the tissues due to gamma globulins that are stored there? Are the gamma globulins held in reserve in the tissues in a state similar to that of the gamma globulins in the blood stream and to those derived from other individuals who have been exposed to comparable infections? Presumably the life of the gamma globulins, as of the red cells and of the plasma albumins, is limited. It is to the structural tissue pattern which determines the formation of the immune globulins with their highly specific properties that we must turn. Our studies of the blood must lead us next to the tissues.

LIPOPROTEINS

Another group of globulins appear to be responsible for the solution and transport of lipids in the body. Knowledge of the chemistry and of the functions of the lipoproteins is only now beginning. We know that most of the lipid is combined more or less loosely with alpha and beta globulins. Fractions have been prepared which are water soluble and which contain over 50 per cent lipid. The lability of these fractions in the state thus far achieved is far greater than is that of albumin or the gamma globulins, of fibrinogen or of thrombin. When dried from the frozen state certain, but not all of them, are denatured and the cloudiness of the resuspended dry plasma is attributable to these substances. Their separation as water-soluble concentrates should open the way to the study of their properties and their role in the economy of the body. The diversity of the fractions that have already been separated suggests a multiplicity of structural types and presumably of biological functions.

THE FRACTIONATION PROCESS

The separation of closely related proteins from each other demanded the development of a new system of fractionation. The large scale process that has been developed and used in the purification and concentration of blood derivatives is based on systematic studies carried out over many years upon the solubility of amino acids, peptides and proteins in alcohol-water mixtures under conditions of varying salt content, pH and temperature.² Alcohol is a protein denaturant at ordinary temperatures, but this effect is minimized if the temperature is sufficiently low. In the present system it is maintained between 0 and -10°C . Alcohols are also protein precipitants. This effect is great at relatively low alcohol concentrations. Further increase in alcohol is often less effective than achieving the optimal acidity for the precipitation of each protein species. The alcohol in our process for plasma fractionation rarely exceeds 25 and never 40 volumes per cent.

Salts increase the solubility of most proteins at reactions between their isoelectric points and neutrality. At very high concentrations certain salts are protein precipitants. Salting out, the classical procedure for the preparation of proteins, plays no part in our process in which the salt content never exceeds that of the blood. Dialysis is thus unnecessary, the protein precipitated being dried from the frozen state to yield stable purified products which can be redissolved at any concentration and in any diluent.

The solvent action of neutral salts is greater the greater the electric moment of the protein and the greater the concentration of alcohol in the system. The balance between the precipitating action of the alcohol and the solvent action of the salt permits attainment of a variety of conditions in which a protein has the same solubility and thus permits a choice of conditions for separating it from other proteins. The solubility of a protein is minimal at reactions near or acid to its isoelectric point. In the case of blood proteins hemoglobin and gamma globulin

² Since 1930 with the uninterrupted support of the Rockefeller Foundation.

are least soluble near neutrality, while albumin and certain alpha globulins are least soluble at acidities one hundred times as great. The balance between alcohol precipitation and salt concentration will thus be different at each pH for each protein species. The pH in these systems is conveniently controlled by buffering the ethanol-water mixtures with acetates or other salts of known ionic strength.

Salt and alcohol concentration and pH are variables which influence the behavior of all proteins. The temperature at which separations are made is a fourth such variable and has been accurately controlled in effecting the completely reproducible separations which have been achieved. The influence of temperature on solubility will vary greatly from protein to protein and will depend upon the other conditions defining its state. Advantage has been taken of high heats of solution to achieve separations and in the case of the albumins to achieve crystallization.

The fifth variable that has been accurately controlled is protein concentration. The presence of each protein component in a complex system must theoretically influence the solubility of every other one. These effects are of many kinds but all increase with increase in protein concentration. In order to minimize protein interactions in the complex system which is plasma separations have been carried out at several times the volume of the plasma. Indeed, the protein concentration in the system of defined pH, temperature, alcohol and salt concentration at which albumin is separated from the alpha and beta globulins is but one-eighth that of the plasma. The resulting albumin has a purity, however, without reprecipitation or crystallization, of over 98 per cent.

An understanding of the interactions between proteins and between proteins and electrolytes is fundamental to our understanding of the mechanism which is the body. The complexity of concentrated solutions in equilibrium with proteins in the solid state imposes variables in addition to those that have thus far sufficed to effect the separations of the plasma proteins. They are, however, similar in nature and susceptible to physico-chemical definition.

These methods are not specific for the blood proteins. They should be useful also in the fractionation of other tissues rich in proteins, carbohydrates or lipids whether of animal or vegetable origin. The conditions for each separation will, however, have to be determined anew in each case. The laborious nature of these physical and chemical investigations, involving as they do, analytical, physico-chemical, physiological and immunological control, do not lend themselves to easy or rapid application to other systems. Nonetheless the tools would appear to be at hand to permit the studies of bodily equilibria begun with the separated and purified blood components to be extended to an investigation of other tissues. In so doing we may hope to approach more closely that understanding of bodily processes at the level of molecular interactions which in the end must form the basis for their control.

CEREBRAL INJURY BY BLUNT MECHANICAL TRAUMA

REVIEW OF LITERATURE

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"Every scalp wound, no matter how trifling, is a potential penetrating wound of the skull." (Cushing, 1918)

CONTENTS

I. The mechanisms of cerebral trauma.....	339
II. The immediate morphological effects of cerebral trauma.....	342
III. The microscopical cerebral injury.. . . .	344
IV. The cerebral trauma not associated with recognizable organic changes.....	347
V. Secondary developments.....	349

A physical visualization of the ways by which injuring forces are transmitted to the brain is essential if the problem of cerebral trauma is to be approached correctly. It is readily understood that the effects of a trauma will vary according to the area of application of the striking force, the degree of plasticity, elasticity, and tensile strength of the part struck, the shape, speed and weight of the injuring agent, and the degree of relaxation of the offended part at the moment of the impact.

I. THE MECHANISMS OF CEREBRAL TRAUMA

In discussing the different patterns of skull fractures, Bruns (1) arrived at the conclusion that if all skulls were equally thick and equally elastic, the lines of fracture could be calculated on mathematic formulas. Actually the skull is not a homogeneous body but is composed of panels of bone, offering variations both in thickness and elasticity from race to race, from individual to individual, and in the same individual in the different portions of the skull. This explains how skull fracture patterns, although subject to some extent to the laws of mechanics, are so varied and unpredictable. The same is true and equally applicable to the cerebral injuries by physical violence, considering that the brain also is composed of tissues of differing specific gravity, toughness and tensile strength.

Moritz (2), in his discussion of the mechanisms of injury by physical violence, has stated that the manner in which a moving force modifies the state of rest of a tissue, or the manner in which the motion of a tissue is changed by meeting a resistance is what determines the fundamental character, type, shape and degree of a mechanical injury. In relation to the mechanism of movement, brain injuries have been said to occur in one of the following two ways: either by distortion of the skull—so-called compression concussion of Denny Brown and Ritchie Russell (3),—or by movements of the brain within the skull as the head is thrown through space and then brought to sudden rest—so-called acceleration concussion of Denny Brown and Ritchie Russell.

In "compression concussion", the skull at the site of application of the force, even though it is not fractured, is likely to be momentarily deformed locally and generally distorted. The result is that the new curvatures of the distorted skull will necessarily impinge upon the underlying brain matter, giving rise to increased pressure in some areas and to diminished pressure in others. As Moritz (2) says, it is apparent that the amount of injury does not depend as much upon the violence of the impact between the skull and the external object as upon the architecture of the inner surface of the bone at the site of impact and the violence of the impact between the skull and the brain.

The effects resulting from the rebounding of the skull, after the injuring force has ceased, must also be considered. As this occurs, the sudden change in the intra-cerebral pressure will cause the meningeal vessels to be pulled away from the brain, evulsed and broken, and the most superficial brain structures to undergo further damage. This explains why an elastic bone, although less likely to be fractured than a rigid one, offers less protection to the underlying brain, as it is more easily deformed or distorted when struck by a force.

More severe effects are to be expected when forces of acceleration are operating. Besides the damage at the area where the force causing acceleration is applied, as the brain is made to slide within its dural covering single anatomical units and perhaps the individual cerebral cells are likely to be distorted and the connecting pathways (corpus callosum, commissures) to be bent, stretched or torn in one direction or another, according to the direction of the forces. Furthermore there is liable to be tearing of blood vessels and evulsion of cranial nerves. The delicate vessels draining the cortical veins into the large venous sinuses and the small arteries which enter the base of the brain are the most likely to be evulsed, because of their fragile walls, thus explaining the frequency of subdural or sub-arachnoidal hemorrhages in the corresponding areas. Rowbotham (4) has shown that lacerations occur most frequently when the brain is pushed forcibly against the highly irregular floor of the anterior fossa or against the sharp edges of the wings of the sphenoid bones.

In the space left vacant by the displaced brain, there will be a zone of diminished pressure. Dott (5) has emphasized the role played by the resulting suction in causing rupture of superficial and occasionally of deeply placed blood vessels.

Denny Brown and Ritchie Russell (3) have recently shown that if the head is prevented from moving at the moment of the blow, no concussion occurs, whereas if even slight movements are allowed concussion takes place. In explanation of this, Holbourn (6), working on a "skull-brain model", has demonstrated that to produce "shear strains" of the skull and its contents a rotary acceleration is necessary. Localized damage in cranio-cerebral injury is attributed to skull distortion, distant damage to rotation of cerebral tissue around regions where the brain is locally fixed in relation to the skull. As a result of this rotation constituent particles of the brain are pulled apart, and if they do not join up properly when the immediate effect of the blow is over nervous manifestations

are likely to follow. Accordingly, concussion is thought to be due to a minimal degree of separation of constituent particles, contusion to a maximal separation.¹

It is apparent that the smaller the area over which the energy of the impact is discharged in a fixed unit of time, the greater will be its intensity. If the area of impact be reduced, a point is soon reached at which the injuring force penetrates the skull. This is the case of the gun-shot wound. The penetration lessens the degree of acceleration to which the skull is subjected. The result is that although penetrating wounds frequently cause severe local damage to the brain, they often fail to produce concussion.

Moritz (2) has emphasized the point that "the energy of an impact may be conducted through delicate tissues without damaging them and still cause extensive damage to a relatively strong tissue because the disruptive forces have been focussed and intensified at some point of mechanical disadvantage". In the case of a hollow structure, such as the skull, the energy of impact is propagated by irradiating waves of motion through meridional lines which "diverge as they leave the site of impact and converge as they approach the opposite pole". At the point of collision of the converging waves, a "contralateral" cerebral injury is likely to occur.

The term "contra-lateral" (or "contre coupe") is generally used in the meaning that a pole of the brain opposite the site of impact has shown some damage; it does not indicate, however, the mechanism by which the injury was produced. Converging of motion waves is one possibility. Another is that of two impacts, the first at the site where the head had been struck by the offending body, the second where the advancing surfaces of the brain were brought to a sudden rest by the forces which resisted its forward motion. The shortening of the axis of the brain along the direction of the traveling force must be considered as a third possibility. This mechanism, as Moritz (2) remarks, can apply to impacts on the sides of the head, because of the relatively high degree of elasticity of the horizontal arch of the skull. It does not seem to apply, however, to occipital or frontal impacts. The longitudinal arch of the skull is in fact less elastic than the horizontal and, unless a transverse basilar fracture occurs, the rigidity of the bones of the base prevents any significant retraction. Furthermore, even though a force tends to progress in the direction in which it was initiated, it also tends to pursue the lines of least resistance and to split up into its components as soon as resistance is encountered. The influence of the strengthening buttresses of the skull and of the dural involucres must be considered also, in explaining why a force traveling in the brain matter in the direction of the longitudinal arch of the skull so often takes an irregular course.

According to Ritchie Russell (7) traction rather than contusion is the actual cause of a contra-lateral injury, as the brain is torn from its coverings by the

¹ Experiments on dogs by Gurdjian and Webster (Surg., Gyn. & Obst., 76: 623, 1913) have recently shown that the pathological and physiological damage produced by a trauma is less marked if the head is allowed to move, but that a greater degree of mass movements of the brain may occur under conditions of a non-fixed head.

force of its own momentum, with consequent stretching and laceration of pia-arachnoidal membranes and blood vessels. This hypothesis explains the contra-lateral subarachnoidal bleeding; it does not account, however, for the extensive laceration both of cortex and membranes so often seen in actual contra-lateral lesions.

LeCount and Apfelbach (8), in a large series—504 cases—of traumatic brain injuries, noticed that contra-lateral injuries were most likely to occur when the head was in motion at the moment of impact, whereas in the resting head the lesion was usually limited to the point of application of the trauma.

One can conclude that cerebral lesions fitting into the definition of contra-lateral injury are likely to occur as the result of different mechanisms which, according to the modality of the accident, may operate singly or in combination. The use of the term contra-lateral injury in a limited sense, to indicate only that an area of brain opposite the site of impact has been injured, appears therefore to be the correct one.

II. THE IMMEDIATE MORPHOLOGICAL EFFECTS OF CEREBRAL INJURY

Any force which deforms the skull locally or causes the position of the brain to be changed suddenly in relation to the skull may result in damage to the meninges, the intracerebral vessels, and the cranial nerves, may contuse or lacerate the brain substance, or may induce a neuronal injury of microscopical or submicroscopical dimensions.

Sequelae of head trauma with frank cerebral involvement are easily appraised. Tanzi and Lugaro (9) were pioneers in describing and interpreting the residual changes from cerebral trauma. We find ourselves, however, more dependent on the investigations of Cajal (10), and Rand and Courville (11) for the very detailed description of changes occurring in contused or lacerated brain tissue. The obliteration of neurons at the zone of impact, the swelling, twisting and fragmentation of fibers situated at the edges of the wound, with formation of end bulbs resolving into free balls which appear early and maintain their identity months and years after the accident, are all well established findings. In agreement with the previous observations by others (Jakob 12, Pfeifer 13, Schwartz and Frick 14, Greenfield 15, Hassin 16) it has already been shown (Tedeschi 17) that degenerative changes in neurons can always be found in cases of fatal head injury not only in the area of contusion but also in remote areas which had appeared unaffected grossly.

These degenerative changes are associated with reactive phenomena ultimately leading to the process of repair. In as much as dead tissue must be removed, the process of repair in the brain does not differ from the same process in other organs. The histological details, however, are peculiar to the special nature of the cerebral tissue.

Following a contusion sufficiently severe to produce pulpefaction of brain substance, the wholesale destruction of cells precludes the possibility of a local tissue reaction. In these cases the process of repair depends fundamentally on a reaction which occurs at some distance from the zone of impact and results in a prompt streaming of microglial elements towards the injured area.

The time of onset and progress of the phenomenon have been traced by Del Rio Hortega and Penfield (18) in the brain, and by Alberca (19) in the spinal cord of experimentally contused animals. Microglial cells were already noticeable in the injured area at the 12th hour and compound granular corpuscles at the 24th hour. Farrar (20) and Linnell (21), under similar experimental conditions, confirmed the rapidity with which the cellular reaction takes place and its persistence as long as degenerated tissue remains in the wound under repair.

A similar sequence of events was described by Rand and Courville (11) in injured human brains. Early changes consisting of swelling of the processes and of the bodies of the microglial cells were already present two hours after the injury, and transitional forms, which might be recognized as stages in the development of compound granular corpuscles, after twenty-four hours. Fully developed granular corpuscles could not be observed, however, either in contused or lacerated brains until almost four days after the injury. Stevenson (22) has pointed out the great disappearance of nerve tissue due to the "eating up" by the phagocytic microglia cells.

Oligodendrocytes, according to the results of investigations by Ferraro and Davidoff (23), also participate in the formation of compound granular corpuscles. This has not yet been confirmed in human material. There is agreement, however, on the rapidity with which these elements undergo acute swelling following a traumatic injury of the brain (Rand and Courville 11). Early changes consisting of the presence of intracellular cytoplasmic vacuoles were already present in a woman (case 19) killed practically outright by a trauma to the head. In another subject (case 15) dying thirteen minutes after the trauma, the oligodendroglia cells showed widespread swelling; and in a third early case (No. 3) forms suggesting direct cell division were present two hours after the accident. From these and other observations, Rand and Courville (11) concluded that acute swelling of the oligodendroglia is an early and almost consistent observation in brain trauma. In cases that had survived the injury longer, swelling of oligodendrocytes was found as long as two weeks and, near damaged areas, thirty-eight days after the accident.

Penfield (24), Penfield and Buckley (25), Pfeifer (13), Wilson (26), Wortis and McCullough (27), all have shown that, as soon as the damaged nerve tissue has been removed, the final healing of the wound is brought about by a proliferation of mesodermal elements from neighboring blood vessels and particularly from those at the surface of the brain. This seems to be the rule when there has been extensive loss of tissue. When, on the contrary, the local damage was milder, most of the repair is accomplished by a proliferation of glial cells (Hassin 16). Penfield (24) has advanced the opinion that the damaged nerve tissue itself provides the stimulus for the astrocytic reaction. The development of this reaction has been traced by Linnell (21) in its successive stages. At the third day hypertrophy of the cell bodies was already noticeable and at the fourteenth day the astrocytic processes were definitely oriented towards the margins of the wound. It was only at the fourth week that a clear "felting" could be observed and after two months that the glial network had thickened so much as to represent what has been called the actual "protective scar".

The question of the primary or secondary nature of the hemorrhagic changes so often accompanying the softening of brain matter in the contused areas is still debated. As the brain slides within its dural coverings, tearing and evulsion of blood vessels is likely to occur under the force of the impact, but this does not seem to be the case invariably. In Jakob's series (12), for instance, the hemorrhages were rare, so that, in discussing the effects of blunt impacts on the head of animals struck while under narcosis by a hammer falling of its own weight on the parietal region, he decided in favor of the secondary nature of the hemorrhagic changes and attributed them to the softening of brain matter noticeable not only at the zone of impact and its immediate vicinity, but also far beyond it, in the mid-brain, pons, fourth ventricle, and even in the upper cervical cord, when the trauma had been applied to the parietal region.

III. THE MICROSCOPIC CEREBRAL INJURY

When the pathology underlying the brain injury is clear, the inescapable conclusion is that as the result of the trauma a condition has been created which is directly responsible for the clinical symptomatology presented by the victim. The functional effects of an injury, however, are by no means invariably associated with morphological changes of corresponding severity.

Trotter first (28), then Symonds (29), and Russell (7) have taken the duration of loss of consciousness at the time of the accident as an approximate measure of the degree of cerebral damage. In general it has been stated that the greater the damage to the brain the longer the period of unconsciousness; but this is far from having been demonstrated. Bennet (30), in his classification of the milder forms of brain concussion, considers a sub-group 4 in which loss of consciousness does not occur at all. There are in addition a number of recorded and perhaps a greater number of unrecorded cases in which a subdural hematoma, an epidural hemorrhage, hemorrhage in the subarachnoidal space or even a contused laceration in the brain substance was found at operation or on postmortem examination of the body following a head trauma in which there had not been a history of even a momentarily dazed state (Ruhe 31, Neuberger 32, Thomas 33, Smidt 34, Mendel 35, Strauss and Savitsky 36, Globus 37). Leri (38) has reported a large number of cases of brain injuries by small shell or bone fragments, or even by bullets piercing the skull, that had produced definite damage but that had failed to induce unconsciousness. Similar observations have been related by Horn (39), and Josephowitch (40) has gathered several cases of post-traumatic epilepsy in which there had been no history of unconsciousness at the time of injury. Most recent is the case of Olivecrona (41), of a young woman with a typical epileptic syndrome which could be traced to an injury to the head received in early childhood and considered trivial at the time.

Among the changes of the minor type which were taken to account for temporary loss of, or perverted functioning, evidence of damage in the ganglion cells was reported as far back as 1870 by Virchow (42) and later re-investigated by Budinger (43), Von Sarbo (44), and Rossi (45). Meyer (46) emphasized the presence of small foci of cortical softening and the absence of marginal glia

beneath the point of injury. Döring (47) called attention to the loss of oxidase ferment. To the same category of minor findings pertain the neuronal changes recently described by Tedeschi (17) in rats recovering from a temporary period of unconsciousness following a blunt impact on the head which had left skull and brain apparently intact. Thickening, spiroid course, and at times definite twisting of the axons of the cortical cells were already apparent in the animals killed at the first hour. The corresponding nerve cells showed obscuring of the cell outlines, tigrolysis, and huge peripheral vacuoli, suggesting pericellular edema. Groups of these cells alternated with others displaying normal cellular patterns and axis cylinders pursuing their usual straight course. The same type of focal damage was displayed by the medullated axons, which appeared poorly impregnated, with a corresponding moniliform swelling of the myelin sheaths. More advanced myelin disintegration and neurolysis were found in the animals killed from the fourth to the 72nd hour, which showed marked corkscrew twisting and fragmentation of the axis cylinders, incipient myelin reabsorption and resolution into fat globules. Where demyelination and breaking down of axons was still in progress a quantitative increase of microglia cells was noticed, and evidence of glial reaction, mostly without appreciable increase of glial fibers, was detectable in the later stages.² These findings suggest that concussion may be due to neuronal injury seen by histological methods. However, since one cannot rule out the possibility that these changes are secondary to other conditions primarily involved in the phenomenon of concussion, nothing more definite can be claimed at present.

It is apparent that nerve cells and nerve fibers may be affected by a number of pathological factors following a mechanical violence to the head. Among these, cerebral edema has been considered by some, (Hassin 16), while others gave more stress to multiple petechial hemorrhages, which, lacking evidence of any other striking change, were felt to represent the main finding in fatal cases of concussion. Some authors (Neugebauer 48) have gone so far as to attribute to them the cause of unconsciousness. We are indebted to Bright (49) for first having pointed out this finding, soon confirmed by the observations of Rokitsansky (50), Blandin (51), and Foerster (52). Later Duret (53) called attention to the most frequent localization of the hemorrhages in the medulla oblongata and corpora restiforma. He thought that the reason for this prevalent localization was to be found in the fact that at the level of these formations the wave-like forces elicited at the site of the impact came to intensification, causing rupture of blood vessels and bruising of the ventricular walls.

The apparently more frequent localization of the foci of hemorrhage in these brain regions in people with a history of concussion made some consider the possibility that the center for consciousness rested just in these areas. Ac-

² In agreement with these observations are the recent findings by Windle, Groat and Fox (Surg., Gyn., & Obst., 79: 561, 1944) of disorganization of the pattern of the Nissl bodies, shrinkage and progressive chromatolysis, most severely affecting the large nerve cells (such as those of the red and lateral vestibular nuclei), in guinea pigs submitted to brain concussion.

cordingly, Penfield (24) thought that lesions about the thalamus were more apt to lead to unconsciousness than lesions elsewhere, and a similar opinion was advanced by Greenfield (15).

The predominance of the foci of hemorrhage in these determined regions was found, however, not to be constant. Subcortical petechiae were fairly common in the series of Winkelman and Eckel (54). In Cassasa's five cases (55), the tiny hemorrhages were irregularly scattered throughout the brain matter. Cassasa proposed that over-filling by cerebrospinal fluid driven into the spaces of Virchow-Robin by the pressure exerted by the distorted skull was the cause of the hemorrhages, due to the tearing of the vessel walls at the sites of attachment of the fibrils which pass across these spaces. Later Martland and Beling (56), in describing nine more cases, remarked that the frequency of the condition in cases with intact skull was higher than in cases with skull fracture, as the splitting of the bone envelope at the time of the trauma had prevented the increase of intracranial pressure and consequently the displacement of cerebrospinal fluid.

The mechanism of production of punctate hemorrhages, as explained by Cassasa (55), has not however been unanimously adopted. Greenacre (57) pointed out the great pressure ("4-11 atmospheres, or 16-44 times the normal pressure") necessary to rupture an intact blood vessel. In addition, it has been objected that the existence of perivascular spaces is not yet demonstrated. According to Hassin (16), the subarachnoid space is not open, but is a "dense, sponge-like connective tissue structure", and the Virchow-Robin spaces are "only potential capillary spaces enclosed within the connective tissue, adventitial tunics of the capillaries, veins and arteries". If Hassin's view is accepted, it seems unlikely that even severe blows can displace the cerebrospinal fluid from the subarachnoid spaces into the virtual net of the intercellular channels.

Other explanations have therefore been advanced. Dietrich (58) has proposed that endothelial injury by vasomotor disturbance is the cause of ring-hemorrhages. Ricker (59) attributed them to vascular engorgement, followed by asphyxia and then diapedesis. The same opinion was expressed by Berner (60). In discussing the finding of punctate hemorrhages in association with various diseases, Baker (61) claimed that the condition is due to rupture of tiny capillaries surrounding the larger vessels. Cornwall (62), who had the chance to examine the sections of one of Cassasa's cases, suggested that the hemorrhages were due to fat embolism. Shaller, Tamaki and Newman (63) more recently interpreted the findings as occurring by diapedesis through the walls of blood capillaries injured by circulatory stasis.

It is clear that both cerebral edema and petechial hemorrhages may account for degenerative changes in neurons by disrupting the original relationship between the single anatomical units and their connecting pathways; but identical changes in neurons have been described (Tedeschi 17) when there was no evidence of either of these conditions.

In considering the influence of other "shear strains", Cajal (10) has emphasized the susceptibility of the neurons of young experimental animals to the effects of minimal amounts of trauma, with the absence of other changes. Rand and

Courville (11), in human material, also have suggested the possibility of rupture of nerve fibers as the only result of the "shock of the injury", and Greenfield (15) has pointed out the facility with which the neurons may be bent, stretched or torn whenever the brain is made to alter its shape. From a mechanistic standpoint, it may be assumed therefore that the more severe the "shear strain" the greater the amount of neuronal damage, thus explaining why forces connected with movements of the brain within the skull, causing the most pronounced "shear strains", are followed by ill effects more frequently than when forces of this type are not involved. The part that these neuronal changes will play in the development and in the persistence of late-appearing disorders of cerebral functions will necessarily depend on the location and extent of the neurons involved, on the possibility of a redistribution of impulses through undamaged pathways and of repair in neurons affected by a lesion of a reversible type.

IV. THE CEREBRAL TRAUMA NOT ASSOCIATED WITH RECOGNIZABLE ORGANIC CHANGES

Since the well known observations by Litré (64) in 1705, of a young criminal who threw himself against the prison wall, dying immediately, and did not show at the postmortem examination any evidence of skull or brain injury, the occurrence of a temporary and even of an irreparable loss of cerebral functions following a trauma to the head in which pathological examination of the brain failed to offer any plausible explanation has been recorded frequently, (Bergmann 65). Vance (66) has reported an analysis of 512 autopsies in individuals dying of head injury, and has emphasized the lack of any demonstrable injury in 16 cases. The absence of demonstrable changes following a mechanical trauma to the nerve centers has been shown more recently by Miller (67). The failure of trypan blue injected intravenously to stain the cerebral matter of concussed animals was considered by him as an evidence that organic damage had not occurred.

Litré's observations did much to give definite form to the conception of loss of cerebral function due to traumatic "shake-up" of the head without any visible injury. It was, however, a century later that a communication by Petit (68) had considerable influence in directing medical thought toward the theory of purely "non-structural neuronal injury", farther developed by Erichsen (69) with the conception of "molecular disarrangement" of the nerve cells as a cause of diffuse neuronal paralysis.

This theory in its abstract terms and highly hypothetical basis did not satisfy the majority and soon other explanations were proposed. Much thought has been given to the possibility of an acute disturbance in the vascular supply of the brain. Accordingly, Friedman (70) proposed that paralysis of the cerebral vasomotor nerves may account for temporary loss of function and, if protracted, for death. At the time this theory was proposed—1892—the existence of a sympathetic innervation of the blood vessels of the brain had not yet been shown convincingly enough; this conception was therefore considered to be without meaning in terms of known physiological mechanisms. Nowadays,

in the light of Penfield's demonstration (24) of nerve fibers in the walls of the intracerebral blood vessels, and of Forbes' showing (71) of cerebral vasomotor reaction, the theory becomes more plausible. The conception of Friedman (70) was accepted by Courtney (72), who arrived at the conclusion that the condition known as cerebral concussion is due to impairment of the regulating vasomotor functions of the brain. Kuhne (73) expressed a similar opinion and assumed that in cerebral concussion a stimulation of the vasomotor center take place associated with a reflex paralysis of a large portion of the ganglion cells. Also, according to Shaller, Tamaki and Newman (67), cerebral concussion definitely interferes with normal vasomotor function, and, if persistent through successive stages of prestasis, edema and anoxemia, is able to lead to organic damage.

The old theory proposed by Stromeier (74) is similarly based on a temporary vascular disorder but along a different line of thought. Loss of neuronal function he attributed to acute compressive anemia resulting from obliteration of the lumen of cerebral blood capillaries following the sudden flattening and distortion of the struck skull. In a modified form this view was later taken up by numerous authors. It appears in the monograph of Kocher (75), and has been repeatedly emphasized by Trotter (28) who ascribed the temporary nature of the condition to gradual recovery of circulation, through a phase of venous congestion, leading to hyperexcitability of the neurons.

That mechanical stimulation of a pial arterial vessel will cause it to constrict has been shown by Florey (76), and confirmed by Echlin (77) who applied the method to the experimental reproduction of patchy cerebral ischemia. The stretching of the vessel itself appeared to be an adequate stimulus to produce constriction, which usually occurred only over the vascular area stimulated. As the spasms did not propagate themselves, the conclusion was reached that they were muscular in nature and independent of nervous reflexes, central or local. The clinical significance of these experimental observations depends on whether they are representative of what happens in the human brain under similar conditions. Riser (78) has described the constriction of a single human pial vessel under mechanical stimulation. If this could be confirmed, a vascular response similar in nature but on a much larger scale might be suspected to occur in blunt cerebral trauma, either when the new curvatures of the under surface of the distorted skull impinge upon the underlying brain matter, or when the brain put into sudden motion by the striking force is pushed forcibly against the irregular surfaces of the inner skull.

The rôle played by variations from the normal of the intracerebral pressure in the development of the phenomena accompanying the loss of consciousness following a trauma to the head has been given much attention.³ Kramer (79)

³ In a survey of acute craniocerebral trauma McConnell (Brain, 65: 266, 1942) has reviewed the conditions which cause the brain to swell. Intracerebral hemorrhage or congestion of the cerebral vascular tree and swelling of the cerebral tissue by extravasation of fluid in the cells or intercellular spaces are considered to be the main causative factors. White and associates (Ann. Surg., 118: 619, 1943) in a carefully controlled series of experiments on cats have reached the conclusion that when cerebral concussion is produced for

has shown that a transitory abolition of respiration can be observed in concussed animals and has advanced the opinion that this is due to a collapse of cerebral vessels caused by a momentary compression of the brain and consequent increase of intracranial pressure. Similar effects were observed by Maassland and Saltikoff (80) in dogs when a pressure had been exerted on the bare dura. In Cushing's observations (81), blanching of the cerebral cortex, cessation of respiration, and loss of consciousness followed an increase of intracranial pressure and as soon as it was released a return to normality was readily noticed. Also the old demonstration by Ferrari (82) of the possibility of breaking up small glass threads imbedded in the brain matter by striking hard on the skull is in favor of an increase of intracranial pressure in head trauma. It has been estimated (Scott 83) that a momentary elevation of the intracranial pressure above that of the systolic blood pressure is sufficient to produce loss of consciousness. Russell (7), however, has pointed out that an increase in intracranial pressure is not always demonstrable in the concussion period while it is at times noticeable during the stage of recovery when the patient has regained full control of mental activities.

Approaching the problem from a different angle, Denny Brown and Ritchie Russell (3) have recently come to the conclusion, very favorably accepted, that "Excitation, excitation with reflex paralysis, excitation followed by complete paralysis, and complete paralysis alone" are the four degrees of nervous manifestations in which a head injury can be resolved. These stages appeared to be most clearly manifested in the respiratory mechanism, but by analogy it was deduced that they could be applied as well to the neuron on the whole. A generalized "molecular reaction", reversible in type and of a degree not likely to be observed under the microscope, was held to be underlying the concussion state of short duration followed by recovery; whereas failure of blood pressure, as in primary surgical shock, was thought to account for the fatal course of events in the mortal cases. Concussion was therefor defined as "the occurrence of an immediate traumatic paralysis of reflex functions, which occurs in the absence of visible lesions in the nervous system".

The old statement of Savory (84), that "death is due to the shock of the violence rather than to the lesions," obscure in its abstract terms at the times it was pronounced—1869—might find an explanation in the light of the physiological mechanisms shown by later studies.

V. SECONDARY DEVELOPMENTS

So long as brain areas the function of which is essential are not irreparably damaged outright, and if other factors do not intervene, the natural tendency will be towards the healing of the wound. Secondary developments, unfortunately, are very frequent.

Among these, *cerebral edema* has been much emphasized. Hassin (16) says

even brief periods there is an increase in the volume of the brain up to a maximum of 5.5%. Extravasation of fluid through the capillary walls was found to be the only factor responsible and the condition was seen to be not sufficient to produce any of the histologic changes which have been commonly regarded as characteristic of cerebral injury.

that it plays a more important rôle in cerebral trauma than microscopical bruises of brain matter or petechial hemorrhages, so much stressed by other investigators. The same opinion was expressed by Levinson (85) who concluded an analysis of the brain findings in 213 cases of head injury by affirming that cerebral edema is at times the only finding available to explain death. Doubts have been raised, however, as to the real frequency of the process (Moritz 2, Rowbotham 4). If the diagnosis of cerebral edema is reserved, as is proper, for the cases displaying increase of fluid in the perivascular and pericellular spaces, in the light of recent observations this condition seems to be less frequent than it was thought to be in the past. It is likely that in many observations "swelling of the brain" due to hydration of the cells themselves (Rand 86, Rand and Courville 11) or to excess of cerebrospinal fluid in the cerebral ventricles or in the subarachnoidal spaces had led the observers to the incorrect diagnosis of cerebral edema. Shapiro and Jackson (87), in a series of measurements of the water content of traumatized brains, have arrived at the conclusion that, although the brain is frequently enlarged after head injury, the enlargement is caused by ventricular dilatation and blood engorgement rather than by actual edema.

A localized and a generalized edema have been described, and various hypotheses have been advanced to explain their occurrence. Linnell (21) thought the cause was disruption of the attachments of the astrocytes from the walls of the blood vessels. Rand and Courville (11) attributed the condition to stimulation of the secretory activity of the choroid plexuses and of the ependymal cells, possibly due to paralysis of the vasoconstrictor nerve fibers with which these formations are provided, (Findlay 88, Mott 89). How the fluid secreted in excess is able to reach the perivascular and pericellular spaces is not clear, however, unless one accepts Weed's view (90) of the existence of potential communications between the perivascular and pericellular spaces. If this is true, it may be conceived, as Rand and Courville (11) think possible, that the waves of fluid forced down into the perivascular spaces may work their way against the stream, reaching and overfilling the pericellular spaces. A different explanation was advanced by Cannon (91), who attributed the condition to osmotic disturbances, with increased capillary permeability, either due to vasomotor paralysis or to the presence of metabolites in abnormal amounts in the interstitial spaces. Once the condition is set up, venous congestion will naturally aggravate it. As Rowbotham (4) says, a vicious cycle will so result—"edema leads to increased intracranial tension; this causes a venous congestion and venous congestion by causing further capillary stasis increases the edema." How much this secondary development may interfere with recovery, embarrassing the cerebral circulation and consequently the nutrition of the neurons, does not need to be stressed further.

External hydrocephalus is another occurrence frequently mentioned among the conditions complicating a cerebral trauma. Faulty absorption of cerebrospinal fluid due to blockage of pacchionian granulations by extravasated blood is the explanation advanced by Wortis (92). Another, already mentioned, is that of Rand and Courville (11) of an increased secretion of cerebrospinal fluid due

to abnormal activity of choroidal and ependymal cells. An *internal hydrocephalus* has also been described, though less frequently, and two varieties have been recorded. One is an acute form, due to the obstruction of the Sylvian aqueduct either by clotted blood or by sloughed off brain tissue (Ford 93), and the other is a slowly developing form (Moritz and Wartman 94) due either to stricture of the Sylvian aqueduct consequent to bruising of its walls or to obstruction in the roof of the fourth ventricle from organizing extravasated blood. It follows that in both aforementioned conditions, whenever expulsion of cerebrospinal fluid or of blood from the intracranial cavity is not farther possible, brain units are likely to be forced through the openings of the hiatus tentorii or through the foramen magnum. An increase of pressure in the posterior fossa may lead to herniation of the cerebellar tonsils through the occipital foramen with resulting compression of the medulla oblongata, (*cerebellar pressure cone of Cushing* 81). Herniation of brain tissue (in general segments of temporal lobes) through the tentorium openings is another possibility (*tentorial pressure cone of Jefferson* 95). In association with uncal herniation, Evans and Scheinker (96) have described infarction in the course of the posterior cerebral artery resulting from kinking of the vessel walls.

Even the formation of the protective scar may or may not represent the final result of a contusion. As Penfield (24) has pointed out, the scar resulting from the healing of the wound may eventually destroy a portion of cerebral tissue larger than that primarily injured at the moment of impact. Furthermore, a *delayed degeneration* of nervous elements has been shown to take place occasionally weeks, months, or even years after the injury has occurred (Rowbotham 4, Ricker 59). In some instances, changes in blood vessels were found to account for the condition, (Eck 97, Rosenthal 98); in others, in which demonstrable lesions were not apparent (Helfand 99), anoxemia, caused by reflex vasomotor derangement, was held to be responsible for the process. It is not clear whether there is any relationship between this late softening and the condition known as *delayed apoplexia*. This refers to the occurrence, first described by Bollinger (100), of a sudden intracranial hemorrhage some time after a head injury has been sustained—from 12 hours to 5 months according to Marburg (101).

The phrase "*postconcussional state*", or rather, as Brock (102) proposed, "*postcontusional state*" is often used. This refers to certain well known sequelae of head trauma. It is not intended to go into any detailed consideration of the psychiatric aspects of head injury here. A few general remarks, however, may round out the presentation. Strümpell (103) was the first—1888—soon followed by Friedmann (70), Vibert (104), and Koeppen (105) to make clear the distinction between postcontusional state due to organic changes within the nervous system and that secondary to psychogenic factors. Later Neel (106) remarked the similarity of the mental changes following a head trauma to those in other organic diseases of the nervous system, and Horn (39) described clearly the syndrome of terror-neurosis (*Shreckneurose*) as distinct from the organic post-contusional neurosis (*Kommotionsneurose*); as soon as the need for separate

treatment of histogenic and psychogenic disturbances was recognized, suggestions for practical ways of differentiating the two conditions appeared in the literature (Strauss and Savitsky 36, Goldstein 107, Strauss 108).

For the consequences of head trauma for which a background of cerebral lesions could be suspected, Tromner (109) suggested the term *encephalopathia traumatica*. Later Osnato and Giliberti (110) did much to give definite basis to this conception. From the study of one hundred clinical cases of head trauma, with or without evidence of external injury or skull fracture, and of one of Cassasa's cases from a histological standpoint, they arrived at the conclusion that apparently minor head traumata may be also followed by cerebral damage likely to lead to sequelae able to simulate clinically encephalitic syndromes. They felt therefore that the "postconcussion neurosis" should more properly be called *traumatic encephalitis*.

Morphological evidence in support of this conception has been accumulating slowly, perhaps because the cerebral lesion that one expects to see with the naked eye is not found in the majority of the cases at the postmortem examination and further microscopic studies, with the proper methods, are rarely carried out on the apparently negative material.

In the light of recent observations (Tedeschi 17), the question arises as to how many of the so-called "psychogenic post-traumatic disorders without demonstrable brain pathology" would have been classified differently if a thorough histologic investigation of the brain had been done. In connection with this, the twelve cases of birth injury of the brain reported by Benda (111) are important, as the microscopic study of the sections revealed a definite pathology, the existence of which was not suspected at the gross examination of the apparently normal specimens.

In the same category of microscopic changes belong the calcification of ganglion cells and of capillary walls described by Eck (98) in individuals that had previously received a generalized cerebral trauma. Rosenthal (99) confirmed these findings, and pointed out the formation of small disseminated cysts at foci of necrosis. Gliosis or even progressive degenerative changes were thought by Martland (112) to represent the most frequent conditions underlying the clinical syndrome of "punch-drunk", which bears, in his words, "the same relation to multiple concussion hemorrhage as do many of the postconcussion neuroses and psychoses that follow blows or falls on the head."

The behavior disorders in prize fighters described by Martland (112) and later confirmed by Jolk and Gutman (113), Parker (114), Carroll (115), Ravina (116), Winterstein (117), Millspaugh (118), and MacDonald (119) recall those pointed out by Strecker and Ebaugh (120) in children as late results of head injuries of an apparently minor kind. Fatigue was always demonstrable in their series, and the changes in general character and disposition, with hyperkinesis and affective disorders, such as described by Ebaugh (121) in writing of the sequelae of encephalitis, were also explained on the basis of possible cerebral lesions.

In the nervous system, perhaps more than in other organs, it has been much emphasized that there is a wide gap between the amount of injury required to

abolish or to pervert function and the amount required to cause damage of a type that one might expect to see under the microscope. It is already apparent, however, that with advance in technique and more extensive application of present histo-chemical methods this gap is narrowing more and more, so as to allow us to see a not distant future in which the explanation of abnormal conditions, previously attributed to "functional" injury of submicroscopical dimensions, will be found in a demonstrable cellular pathology.⁴

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THE ABSORPTION AND ELIMINATION OF GASES OF THE BODY IN RELATION TO ITS FAT AND WATER CONTENT^{1,2}

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The ease or difficulty with which an individual accommodates to variations in ambient pressure ranging from .10 atmosphere (encountered at an altitude of 50,000 feet) to 15 atmospheres (encountered at a diving depth of 500 feet) is determined by the manner of inert gas exchange characteristic of that individual. In the absorption or elimination of inert gases, the body functions as a rather simple physical system of fluid and fat through which the circulating medium, blood, is the primary means of transport. To understand the principles underlying inert gas exchange, it is necessary to know the solubility and diffusion properties of inert gases in body solutes, the quantities of fluid and fat present, and the rate of gaseous saturation or desaturation in response to variations in ambient pressure.

Solubility coefficients of inert gases.—The body solvents for inert gases are the fluids and fat (table 1). Olive oil, having a coefficient of absorption similar to fat, may be conveniently used for solubility determinations. Of prime importance is the ratio of oil to water solubility since high solubility of a gas in fat in comparison with low solubility in the transport watery medium, blood, delays both its absorption and, following saturation, its elimination. Nitrogen and argon have oil to water solubility ratios of the order of 5.3 to 1 and, by contrast, helium has a ratio of 1.7 to 1. Potent anesthetic gases, e.g., cyclopropane and chloroform, which like gaseous nitrogen behave as chemically inert substances, have ratios of the order of 35 to 1. A sevenfold increase in desaturation time following anesthesia should be required for cyclopropane in comparison with ether (4.3 to 1) or nitrogen. Thus, fat constitutes a huge potential gas reservoir and our first consideration in attacking the problems incident to pressure changes is to estimate the size of this reservoir.

The composition of the body.—In the estimation of fat content, height data and other linear measurements in relation to weight have been of limited value. Since adipose tissue is of low density (0.92 to 0.94) in comparison with muscle and bone, it appeared that determinations of body volume in relation to weight would afford a measure of corporeal and tissue adiposity.

The determination of corporeal specific gravity, however, essentially a relationship between weight and unit volume, had not been utilized as a criterion of the degree of obesity. The essential measurement, that of body volume made by Archimedes, can be conveniently determined by the method of hydrostatic weighing, i.e., equivalent volume equals weight in air minus weight in

¹ Lecture I of The John Wyckoff Lectures on "The Composition of the Body in Relation to Decompression Sickness" delivered at New York University, 7 and 8 December 1914.

² (The contents of this lecture are not to be construed as an official expression of the views of the Navy Department.)

water. Two weighings in water serve to check the accuracy of the procedure, one at the completion of maximal inspiration and the other at the end of maximal expiration. The difference of the two weighings in water serves as a measurement of vital capacity. The hydrostatic determination of vital capacity gives values comparable to those obtained by the standard method employing spirometry.

The additional measurement of residual air serves to correct for a variable which is the greatest source of error in the method. The error due to the presence of gas in abdominal viscera is minimized by the compression of the abdomen following complete exhalation. Repeated determinations on the same individual permitting the use of a constant volume for residual air, and provided that body weight does not change, give values that agree within 4 per cent of the possible range.

TABLE 1

Argon, Helium, Nitrogen, and Oxygen Solubility in Water and in Olive Oil at 38°C., and the Respective Oil Water Solubility Ratios

WATER				OLIVE OIL			
Argon	Helium	Nitrogen	Oxygen*	Argon	Helium	Nitrogen	Oxygen
0.0262	0.0087	0.0127	0.023	0.1395	0.0148	0.0667	0.112

Oil Water Solubility Ratios

ARGON	NITROGEN	HELIUM	OXYGEN
5.32:1	5.24:1	1.7:1	4.9:1

* Van Slyke, D. D., and Sendroy, J.: The Journal of Biological Chemistry, (1934).

In an individual on a restricted diet for a period of 7 months, the loss of 19.5 pounds was associated with a rise in specific gravity from 1.056 to 1.071 and a decrease in abdominal circumference of 4.7 inches. To account for the gain in specific gravity, the tissue lost must have had a density value of 0.937, or a value again in accord with the density of fat.

In a study of naval personnel (1), values for specific gravity varied from 1.021, in obviously obese individuals, to 1.097 in lean individuals. From the data (table 2), specific gravity appears to be inversely related to weight and directly related to the difference between thoracic and abdominal girth when averages for groups were compared.

Thus, the average weight of a group of 38 lean men, 148.7 pounds, was associated with an average specific gravity value of 1.081, and the average weight of a group of 28 fat men, 176 pounds, was associated with an average specific gravity value of 1.056. That the difference in weight of 27.3 pounds is due to fat (specific gravity, 0.92 to 0.94) rather than lean tissue is indicated by the difference (0.025) in the values of specific gravity between the two groups.

If obesity and not weight *per se* is the chief factor tending to produce low values for specific gravity, then a group of heavy but lean men, professional football players, for example, should possess a high average value for specific gravity (2). The group of lean men in the naval service, average specific gravity 1.086, had an average weight of 156.9 pounds. Although the average weight of the football players was 200 pounds, their average specific gravity

TABLE 2

Specific Gravity in Relation to Weight and Difference in Measurements of Thoracic and Abdominal Circumference

SPECIFIC GRAVITY	NUMBER OF MEN	AVERAGE WEIGHT	AVERAGE DIFFERENCE CHEST/ABDOMEN
		lbs.	in.
1.020-1.029	2	233	-0.1
1.030-1.039	2	187	0.9
1.040-1.049	4	166	4.2
1.050-1.059	20	171	4.2
1.060-1.069	23	158	5.2
1.070-1.079	27	153	5.6
1.080-1.089	14	148	6.1
1.090-1.099	7	140	6.9

TABLE 3

High, Intermediate, and Low Specific Gravity Group Values in Relation to Weight and Circumferential Measurements

NO. MEN	AVERAGE SPECIFIC GRAVITY	RANGE	AVERAGE WEIGHT		CIRCUMFERENCE				DIFFER- ENCE IN INCHES	AVERAGE HEIGHT	
			Pounds	Kg.	Chest		Abdomen			Inches	Cm.
					Inches	Cm.	Inches	Cm.			
Naval Personnel											
13	1.051	1.035-1.057	172.3	78.6	37.6	95.5	33.1	84.1	4.5	68.2	173.2
24	1.066	1.060-1.074	166.9	71.3	36.1	91.7	30.6	77.7	5.5	68.5	174.0
38	1.086	1.075-1.096	166.9	71.3	36.5	92.7	29.7	75.4	6.8	69.4	176.3
Trained Athletes Professional Football Players											
25	1.080	1.051-1.097	200.6	91.2	40.0	101.6	33.1	84.1	6.9	72.1	183.1

value was 1.080. The heaviest athlete (specific gravity value, 1.064) weighed 259.5 pounds, or about 100 pounds more than Navy men of corresponding density (table 3). The difference then between the "good" big man who weighs 200 pounds and the "good" little man who weighs 150 pounds, is 50 pounds of flesh and bone but not fat.

Concept of a lean body mass of uniform composition and its relationship to excess fat.—The data thus far presented lead to the consideration that there exists

a lean body mass which has a specific gravity value of 1.011 ± 0.001 , equal to the specific gravity of our leanest men. If the density of this lean mass remains constant, then its composition, with respect to bone and soft tissue, must also be relatively constant so that fat can be regarded as chiefly responsible for departures of specific gravity from the basal value of 1.100 (fig. 1).

Variations in the percentage of bone (10 to 15 per cent) in relation to total body weight might conceivably alter values for specific gravity but it can be computed that such percentage variations in bone weight could alter specific gravity not more than 13 units, a relatively small amount in comparison to the range for naval personnel of 76 units (table 2).

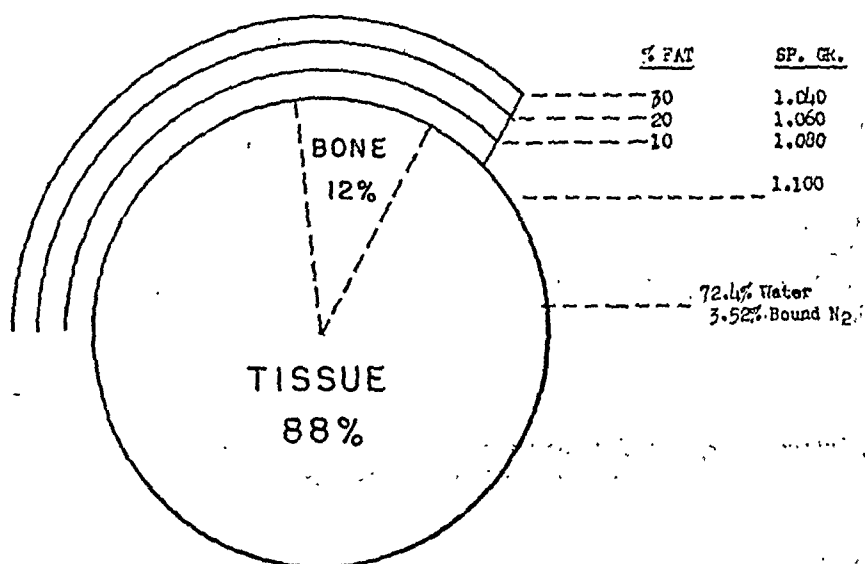


FIG. 1. Schematic representation of the body showing the weight relationships between the excess fat and the lean body mass. The following specific gravity values form the basis for the diagram: fat 0.92, tissue 1.060, and bone 1.50.

If the amount of fat varies inversely with the specific gravity, or

$$\frac{\text{Fat Wt.}}{\text{Body Wt.}} = f \frac{1}{\text{Sp. Gr.}},$$

then the specific gravity of the lean body mass (1.100) will be reduced to 1.080 if 10 per cent by weight of excess fat (specific gravity 0.92) is added, or from 1.100 to 1.060 if 20 per cent of the body weight is excess fat. This simple relationship between specific gravity and excess fat may be formulated in the following manner:

$$\frac{\text{Fat Wt.}}{\text{Body Wt.}} = \frac{10(\text{Sp. Gr. of lean body mass} - \text{Sp. Gr. of whole body})}{2}$$

or,

$$\% \text{ Fat} = 500(1.100 - \text{Sp. Gr. of whole body}).$$

The validity of the concept of the body as comprising a lean body mass of constant composition plus excess fat which is primarily responsible for alterations of tissue density was established during the past year in a precise and meticulous manner by Lieutenant N. Pace and Lieutenant (jg) Edith Rathbun (3) of the

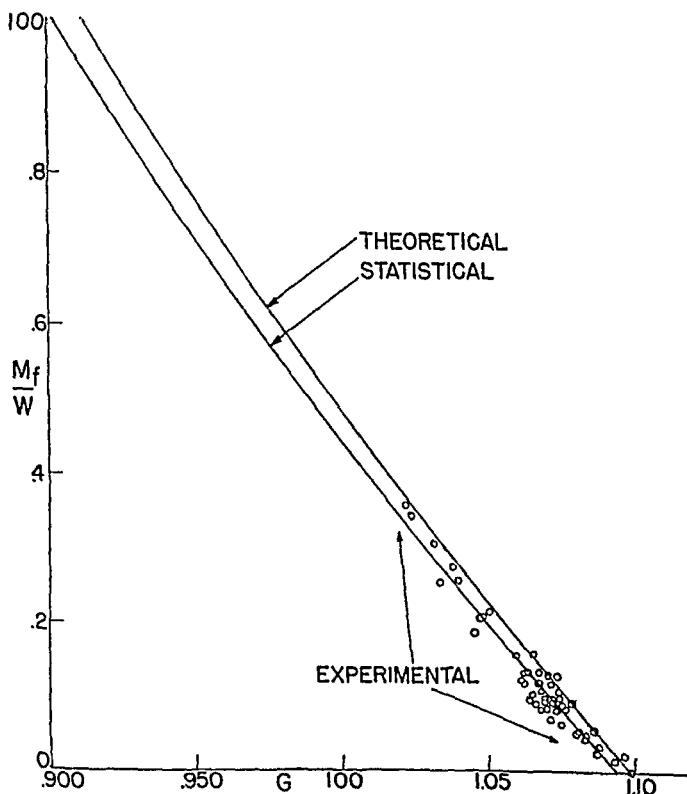


FIG. 2. The grams of fat per gram of eviscerated body weight (M_f/W) are plotted against the body specific gravity (G) for the guinea pig (after Rathbun and Pace, Research Project X-191, Report No. 1, Naval Medical Research Institute).

Naval Medical Research Institute. Using adult guinea pigs of various weights, these investigators obtained the same range of values, 1.021 to 1.097, as were found in man. Aliquot fat-free samples of body tissue including bone yielded a value of 1.098. Furthermore, the inverse relationship postulated as existing between specific gravity and fat content for man was established for the guinea pig (fig. 2).

Composition of the lean body mass.—The density of the lean body mass, 1.099 ± 0.001 , corresponding to the highest values for specific gravity obtained on man was, prior to the work of Pace and Rathbun, arbitrarily divided into 15 per cent by weight of bone, 10 per cent essential lipids, and 75 per cent tissue (4) so that,

$$\frac{W_b + W_f + W_t}{\frac{W_b}{\text{Sp. Gr.}_b} + \frac{W_f}{\text{Sp. Gr.}_f} + \frac{W_t}{\text{Sp. Gr.}_t}} = \text{Sp. Gr. of lean body mass} = 1.099.$$

In view of the analyses of Pace and Rathbun giving values of 1.098 for aliquot samples of fat-free tissue, the small amount of essential fat (in bone marrow and the central nervous system) may simply be included under the category of tissue. Hence,

$$\frac{W_b + W_t}{\frac{W_b}{\text{Sp. Gr.}_b} + \frac{W_t}{\text{Sp. Gr.}_t}} = \text{Sp. Gr. of lean body mass} = 1.099.$$

The determination of the amount of bone in the lean body mass is of prime importance. In three adult guinea pigs, the entire skeleton comprised 12.4 per cent of the lean, hairless mass of tissue (5). For man, an approach to the determination of the relationship between bone weight and weight of the lean body mass is afforded by the ingenious method of Webster (6) by which the volume relationships of bone and tissue in the forearm are measured roentgenographically. Webster's data indicate that measurements confined to the forearm or to the thigh at the gluteal fold give bone-tissue ratios that are representative for the body as a whole. In a study of the forearms of 30 men (7), the following absolute volume relationships between bone, muscle, skin and fat were obtained:

Bone.....	7.12	Muscle.....	70.84
Skin.....	7.45	Fat.....	6.06

The weights of the tissues can be computed as volume times density. Excluding the fat, the percentage of bone in relation to muscle and skin is 11.8 on the basis of a specific gravity value of 1.56 for bone and 1.060 for tissue.

As an approximation based on the roentgenographic measurements and the presumptive information supplied by analyses of the 3 guinea pigs, the lean body mass may be assumed to consist of 12 per cent bone and 88 per cent tissue.

The densities of individual tissues show considerable variation. According to Vierordt (8), values of the order of 1.014 are given for pericardium, 1.122 for tendon, 1.051 for muscle, 1.040 for brain, and 1.057 for liver. Smith and Morales of the Naval Medical Research Institute used experimentally determined values of 1.43 for whole skeleton of 3 guinea pigs previously referred to and 1.066 as the mean value for 30 determinations on muscle.

Blood, however, may be regarded as the building material for lean tissue so that for tissue we may use the specific gravity value of blood, 1.060 ± 0.002 , based on 81 determination on 18 naval personnel utilizing the falling drop method of Barbour and Hamilton (9). Similarly, if the water content of blood, approxi-

mately 80 per cent, is taken as the water content of tissue, then the 20 per cent solid residuum has a specific gravity value of 1.4. For bone, we have used a value of 1.56 computed on the basis of its mineral content and, in lieu of quantitative data, we may use 1.5 as an average value for marrow-free bone.

The concept of a lean body mass of constant composition for corresponding age groups was supported further by the analyses of water and bound nitrogen in the lean body mass of the guinea pig (fig. 3). A linear relationship exists between weight of lean tissue, the bound nitrogen and water content (72.42

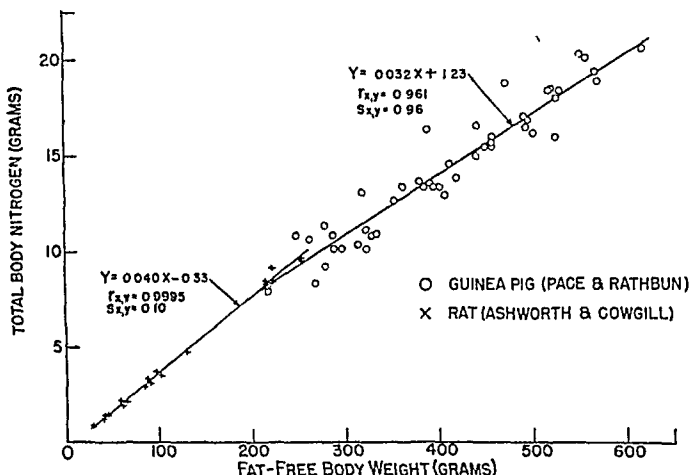


FIG. 3. Total body water plotted against the fat-free body weight for each animal in a series of guinea pigs studied by Pace and Rathbun, and for each animal in the series of rats studied by Ashworth and Cowgill (1938) (from Pace and Rathbun, Research Project X-191, Report No. 3, Naval Medical Research Institute).

($\sigma 2.11$) per cent of the body weight (10)). The composition of the lean body mass may then be presented in the following outline:

	Sp Gr.	% by Wt.
Lean Body Mass	1.099 \pm 0.001	
Tissue	1.060*	88
Blood		
Muscle		
Glands		
Viscera		
Essential fat		
Tendon		
Skin		
Nervous tissue		
Bone	1.5**	

* Based upon the Sp. Gr. of whole blood.

** Computed on the basis of mineral and water content

Species constancy.—The remarkable constancy in water content of the lean body mass has been pointed out by Pace and Rathbun. Values obtained by different investigators for the rat, guinea pig, rabbit, cat and dog range from 69.9 per cent to 74.4 per cent, mean 72.7 per cent. For bound nitrogen, the values range from 3.09 to 3.89 per cent, mean 3.51 per cent (10).

It is probable, therefore, that for man as well as for the species enumerated, there exists a lean body mass of remarkably constant composition as demonstrated by the values for specific gravity and the water and bound nitrogen analyses.

Capacity of the body to absorb gases.—The product of the solubility coefficient of a gas and the respective quantities of solvent present in the body is indicative of the body's capacity to absorb the gas in question. If an individual, for example, inhales oxygen over a period of 9 to 12 hours, the nitrogen originally present in the tissues can be measured as it is eliminated from the lungs. For a diver weighing 70 kilograms, specific gravity 1.060, the nitrogen collected over a period of 12 hours amounted to 1076 cc. (11). The fat in the diver's body can be computed as 20 per cent $((1.100 - 1.060)500)$ times 70 kilos or 14 kilos. The body fluids can be estimated as $.724(70 - 14)$ or 40.54 kilos. The measured nitrogen is in accord with the computed value for nitrogen based on the amounts of solvent present, or,

$$\begin{array}{rcl} 14 \times 55.7 & = & 779.8 = \text{"fat" nitrogen} \\ 40.54 \times 9.0 & = & 364.9 = \text{"fluid" nitrogen} \\ \hline 1144.7 & = & \text{estimated total nitrogen.} \end{array}$$

THE MANNER OF GASEOUS ABSORPTION

Cutaneous diffusion of gas.—The inert gases, principally atmospheric nitrogen, dissolved in the body tissues are transported by the blood mainly from the lungs. Small amounts of gas, however, may enter or leave the blood by way of the skin so that the tissues during the course of oxygen inhalation will never become completely desaturated as long as the skin is in contact with air. Under these conditions, some 15 to 20 cc. of atmospheric nitrogen per hour will be present in the exhaled oxygen.

Nitrogen diffuses even more rapidly into tissues exposed to the air following skin incision. This phenomenon was observed during the course of experiments conducted on anesthetized dogs at the Harvard School of Public Health. Oxygen inhaled by the dog through a tracheal cannula brought about a rather rapid elimination of nitrogen which was expected to be complete in about 4 to 5 hours. After the fourth hour, however, about 10 cc. of nitrogen per hour could be collected for periods of at least 14 hours (fig. 4). What appeared to be a spontaneous generation of nitrogen in the dog's body was found to be a diffusion of nitrogen from the air into the tissues through two incisions, one made for the tracheal cannula and the other made over the femoral artery for insertion of the blood pressure cannula. Closure of these incisions made nitrogen elimination complete in the expected period of 4 to 5 hours and concluded the

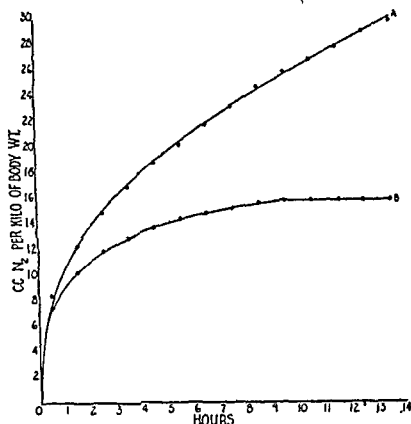


FIG. 4. Curve A represents the elimination of dissolved nitrogen via the lungs of anesthetized dogs with open incisions over the trachea and a femoral artery. Curve B represents the elimination of nitrogen under the same conditions with the exception that the incisions were closed by sutures. The difference between the value on Curve A and Curve B represents the quantity of nitrogen diffusing from ambient air into the dogs' tissues at the areas of incision. (From unpublished data from experiments conducted by Shaw and Behnke at the Harvard School of Public Health in 1934.)

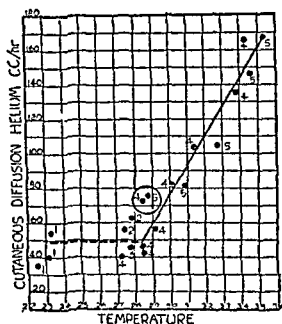


FIG. 5. Cutaneous diffusion of helium in relation to temperature, measured as cubic centimeters of helium recovered from the lungs per hour, when the body is immersed in a helium atmosphere at a pressure of 700 mm. Hg. The numbers, 1 to 5, refer to different subjects. The encircled values were obtained after the previously heated ambient helium had been cooled to 29° C. (From Behnke and Willmon, *Am. J. Physiol.*, 1941, 131: 627.)

attempt to measure the nitrogen of the atmosphere through the tissues of the dog.

The quantity of nitrogen absorbed through the skin, however, is only one-

third to one-fifth the amount that one would expect to recover were diffusion sufficiently rapid to establish equality between the pressure of ambient nitrogen and its pressure in the skin and subcutaneous vessels. By contrast, if the body is surrounded with helium, this rapidly diffusing gas enters the subcutaneous capillaries at a rate sufficiently rapid to allow computation of blood flow to the skin if the quantity of helium collected from the lungs is divided by the solubility coefficient of helium in blood (12).

If the temperature of gas is raised in the bag, a rather sharp break occurs in the absorption curve and a linear rise in helium absorption accompanies the increased temperature (fig. 5).

These experiments illustrate the simple linear uptake of a gas by the blood and its transport to the lungs from which information it is possible to compute peripheral blood flow on the basis of the amount of helium excreted into the lungs and its solubility in blood.

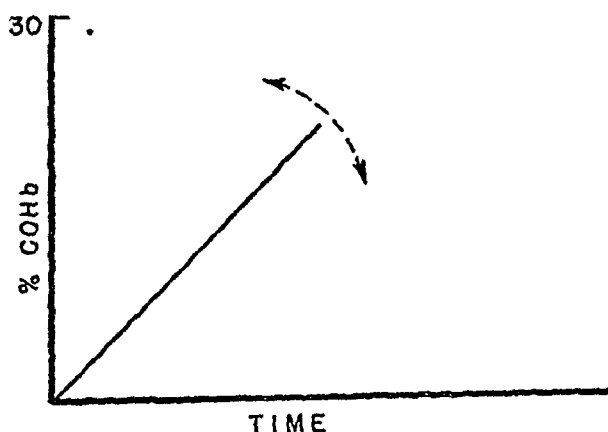


FIG. 6. %HbCO as a function of time. The slope of the line is proportional to the percentage of CO absorbed from the inhaled air.

Absorption of carbon monoxide.—Turning now from the consideration of cutaneous absorption of gas to absorption in the lungs, one is confronted with an entirely different set of conditions. Whereas some 50 cc. of helium can be absorbed through the skin per hour, that quantity can be absorbed into the circulating pulmonary blood within a period of two minutes.

The manner in which the blood absorbs a gas is illustrated by the uptake of carbon monoxide (13). Again, a linear relationship holds for carboxyhemoglobin saturations at least up to 30 per cent (fig. 6). Pace and others have analyzed some of the factors entering into this linear uptake of carbon monoxide and found that, at any given time, t , the quantity of carbon monoxide inhaled will be

$$\text{Min. vol.} \times \text{pts. CO/10,000} \times t.$$

Of the carbon monoxide inhaled, a constant percentage, k , will be absorbed by the circulating blood. The value of k in healthy young men lies between 40 and 50 per cent. If the blood can absorb 20 volumes per cent of carbon

monoxide, then the saturated blood will contain $\frac{\text{Blood volume}}{5}$ cc. of carbon monoxide. The percentage of carbon monoxide absorbed by the blood will then be

$$\frac{100 \times \text{Min. vol.} \times \text{pts. CO/10,000} \times t \times k}{\frac{\text{Blood vol.}}{5}},$$

or, where k equals 0.5,

$$\% \text{HbCO} = \frac{25 \times \text{Min. vol.} \times \text{pts. CO/10,000} \times t}{\text{Blood vol.}}.$$

Of special interest, particularly in patients with pulmonary disease, would be determinations of carbon monoxide removed from the inhaled air under condi

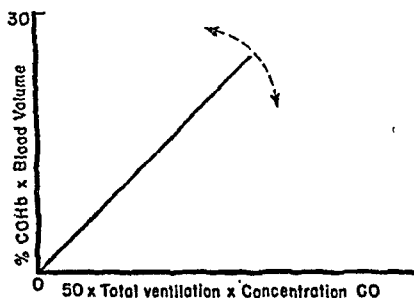


FIG. 7. Total amount of CO absorbed by the blood as a function of the amount available in the inspired air. The slope of the line is proportional to the fraction of CO absorbed in inhaled air.

tions of controlled pulmonary ventilation. The greater the slope of the line (fig. 7), the more effective is pulmonary absorption of carbon monoxide for a given tidal volume. In pulmonary disease, the slope of this line should be decreased.

Manner of absorption or elimination of an inert gas by the body as a whole.—In contrast with the linear absorption of carbon monoxide under the conditions of these experiments, gaseous nitrogen elimination from the body as a whole during the course of oxygen inhalation follows a curve which can be conveniently expressed by one or more exponential terms of the form

$$(1) \quad Y = Q(1 - e^{-kt}),$$

which states that the quantity of nitrogen, Y , is eliminated at a rate which is a constant percentage of the amount present at any given time (14). Q represents the nitrogen content of saturation value at the beginning of oxygen inhalation.

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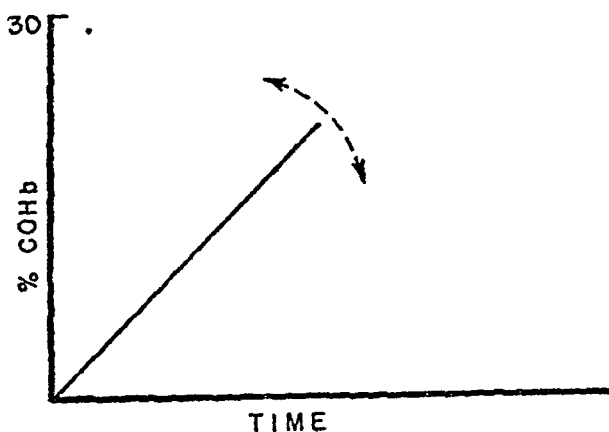


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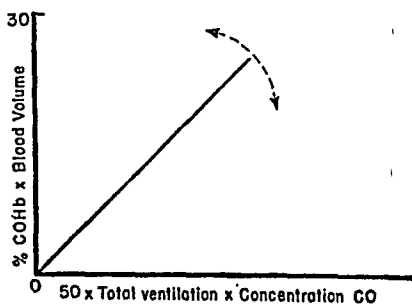


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k governs the rate of change in the slope of the curve, and $(1 - e^{-kt})$ gives the percentage decrease of the total nitrogen during the time interval, t .

The value of Q , in terms of Y , can be expressed as

$$(2) \quad Q = \frac{(Y_1)^2}{2Y_1 - Y_2},$$

provided that the time interval t_2 , corresponding to the value of Y_2 , is twice that of t_1 , corresponding to the value for Y_1 .

In terms of k , equation (1) becomes

$$(3) \quad k = \log_e \times \frac{A}{A - Y} \times \frac{1}{t}.$$

Meaning of the exponential curve.—If the values for nitrogen elimination could be obtained from the single exponential expression (1), then blood flow, in order to carry away, let us say, 5 per cent per minute of the amount of nitrogen avail-

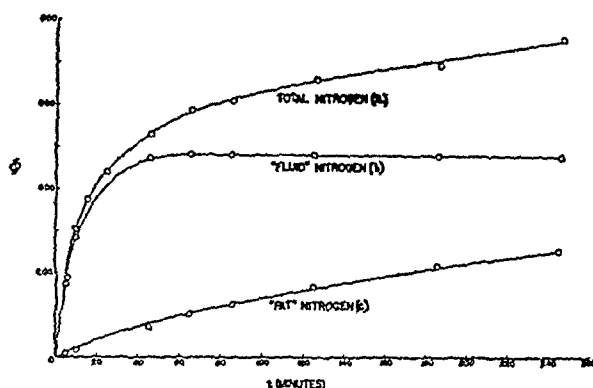


FIG. 8. Elimination of nitrogen from the body during a course of oxygen inhalation. Curve a is drawn through the experimental values. Curves b and c are hypothetical and represent the elimination of nitrogen from the body solvents, "fluid" and "fat." The values of Curve a are the sum of the corresponding values on Curves b and c .

able for transport at any given time, must be distributed uniformly in relation to the nitrogen content of the body. This, however, is not the case for the body as a whole. Areas rich in fat and high in nitrogen content have relatively poor blood supply. Hence, the blood, in the course of tissue desaturation is not carrying equal amounts of nitrogen from the various tissues since the venous blood draining these tissues may, in some parts of the body, be saturated and, in other parts, relatively nitrogen free. The percentage of nitrogen removed in unit time in proportion to the amount present, therefore, is highest at the beginning of nitrogen elimination and gradually decreases during the course of desaturation. If the experimental values for nitrogen elimination are substituted in equation (1), the value of k does not remain constant but progressively decreases from approximately 0.04 to 0.014 during the course of five hours.

The curve for total nitrogen (Curve a , fig. 8) can be more accurately represented by two exponential expressions on the basis of a high value for k during

the first hour and a low value for k after the first hour. If that portion of the curve after the first hour is extrapolated to the left on the basis of its k value, then Curve c (fig. 8) can be drawn. The difference in the nitrogen values for Curve c and those of Curve a is represented by Curve b. Curve a is thus the sum of two components, Curves b and c, or,

$$Y = 480(1 - e^{-.091t}) + 360(1 - e^{-.005t}).$$

The semilogarithmic plot of $(Q - Y)$ and t renders b and c straight lines (fig. 9). The theoretically correct fit of Curve a may be obtained, as Smith and Morales have shown, by three exponential expressions or one more than the number of gas solvents, i.e., fluid and fat (fig. 10).

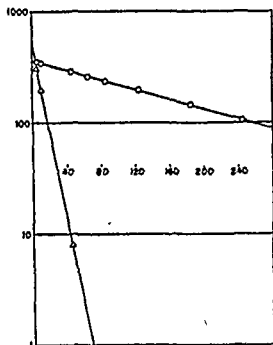


FIG. 9. Logarithmic analysis of Figure 8. If the y values of Curves b and c are subtracted from their corresponding Q values, the $\log (Q - y)$ plotted against time is linear. The Q value for Curve b is 480 and the k value .091. The corresponding values for Curve c are 360 and .005. (From unpublished data of Behnke obtained in 1934-35.)

The interpretation placed upon the "fat" and "water" curves.—The curves b and c (fig. 8) are only approximations of the manner in which nitrogen is absorbed by, or eliminated from, its chief body solvents. They should not be interpreted to mean that fat and water exist as separated entities in the body, but rather that the fat, lipoids, and water are so distributed that during saturation a large part of the nitrogen absorbed by fat and lipoids diffuses from the body fluid (15). On decompression the reverse process is thought to occur. Thus, during decompression following partial saturation, the diffusion of nitrogen from the rapidly saturating body fluids into the slowly saturating lipoids and fat tends to equalize the partial pressure of nitrogen in the different tissues of the body. With the exception of tissues with a high fat content (adipose tissue, bone marrow and spinal cord) the division of the body into tissues which saturate or desaturate at different rates is largely arbitrary and the body can be regarded essentially as a unit. This fundamental concept can be made more clear by comparing the body to a beaker of water in which is distributed fat, with a greater concen-

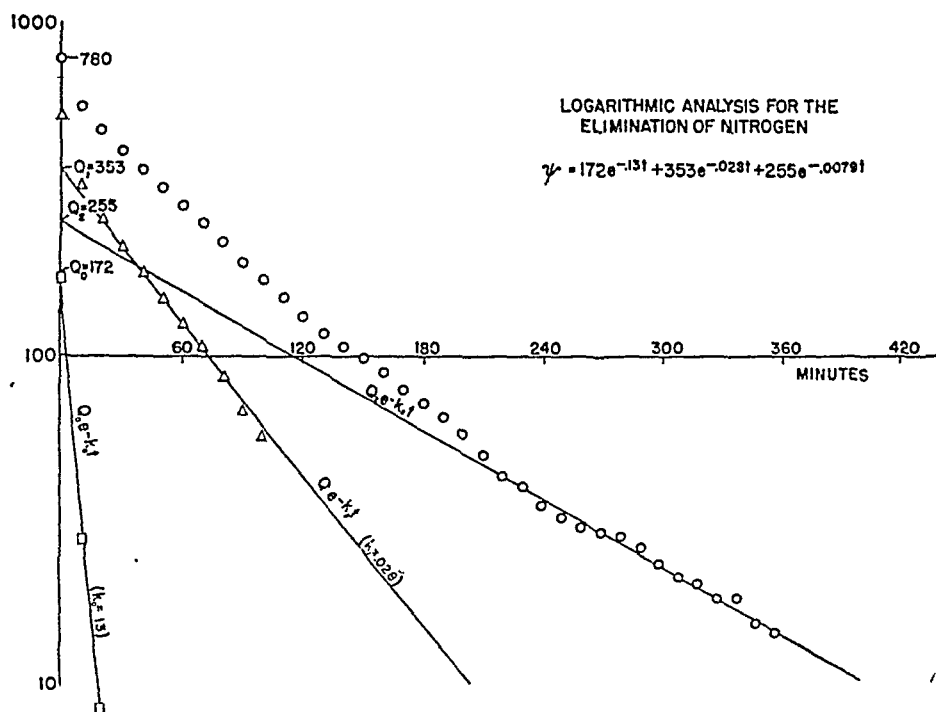
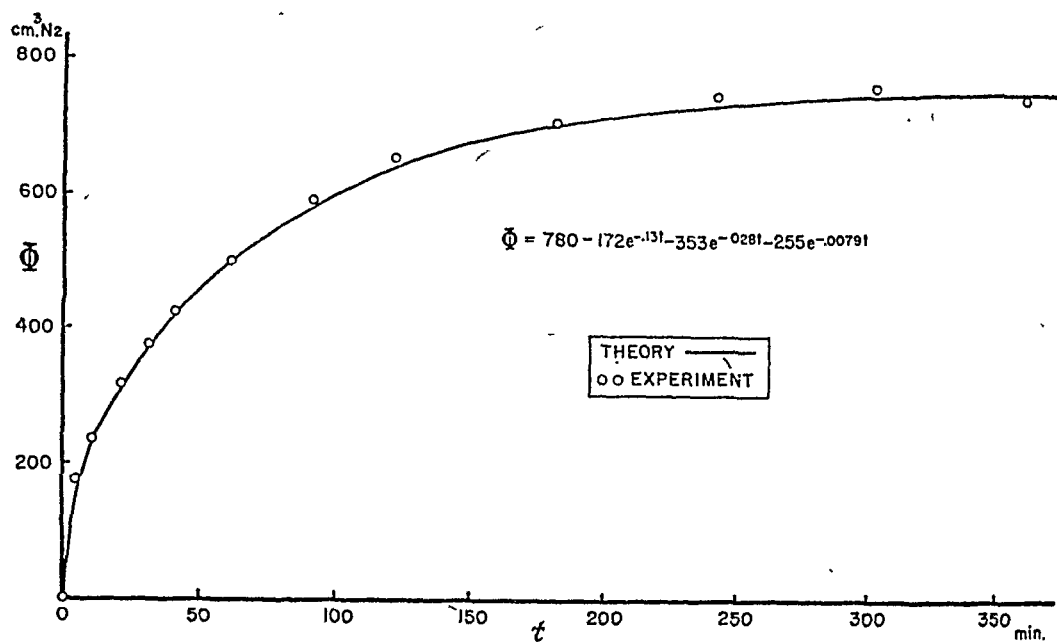


FIG. 10. Semilog plot (lower graph) of a nitrogen elimination curve (upper graph). The total nitrogen eliminated, Q , equals 780 cc. The values on the original curve are the sum of the corresponding values of the linear curves having respective Q and k values of 172, .13; 353, .028; and 255, .0079. (From data of Behnke as analyzed by Smith and Morales.)

tration of fat in the lower portion. If the beaker is now exposed to a high nitrogen pressure for a short period of time and then quickly returned to atmospheric pressure, diffusion of nitrogen will take place from the water into the

surrounding air and also into the unsaturated water and fat present in the beaker. In the body, after short exposures (up to 30 minutes) to high pressure, the fat acts as a nitrogen absorbent during decompression and serves as a buffer against bubble formation in the blood stream. Fat men, consequently, with

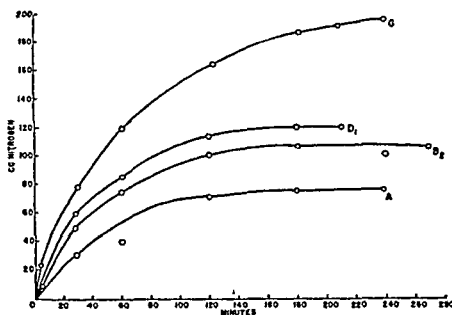


FIG. 11. Nitrogen elimination from 4 dogs placed in an oxygen atmosphere at normal pressure. During the first 7 minutes of oxygen inhalation, the lungs and apparatus were rinsed free from nitrogen. (From Shaw, Behnke, Messer, Thomson, and Motley, *Am. J. Physiol.*, 112: 545 (1935).)

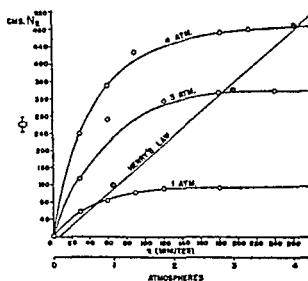


FIG. 12. The nitrogen elimination from the same dog following equilibrium exposures in air at 1, 3 and 4 atmospheres of pressure on different days. The nitrogen eliminated during the first 8 minutes of oxygen inhalation was not collected. Curve A, desaturation from 1 atmosphere; Curve B, desaturation from 3 atmospheres; Curve C, desaturation from 4 atmospheres. Experimental values are indicated by o and theoretical values by x. (From Shaw, Behnke, Messer, Thomson, and Motley, *Am. J. Physiol.*, 112: 545 (1935) (redrawn by Morales).)

adequate blood circulation should be better suited for short exposures in compressed air than lean men.

Elimination of nitrogen previously absorbed at high pressures.—If anesthetized dogs are placed in a closed system of circulating oxygen, the nitrogen elimination curves obtained (fig. 11) reflect individual differences in that desaturation of

the fat dog G is prolonged in comparison with desaturation of the lean dog A (16).

If measurements of nitrogen elimination are made on the same dogs following saturation exposures at 3 and 4 atmospheres, then the quantities of nitrogen removed, in comparison with values obtained at 1 atmosphere, are in accord with Henry's Law (fig. 12).

The helium elimination curves.—If the lipid substances are responsible for the prolongation of helium absorption or elimination, then helium, possessing a low fat solubility coefficient and a more rapid rate of diffusion, should be eliminated in a shorter period of time. Following exposure in a helium-oxygen atmosphere, it is observed (fig. 13) that the absorbed gas leaves the body in about one-half the time required by nitrogen (11). Smith and Morales found,

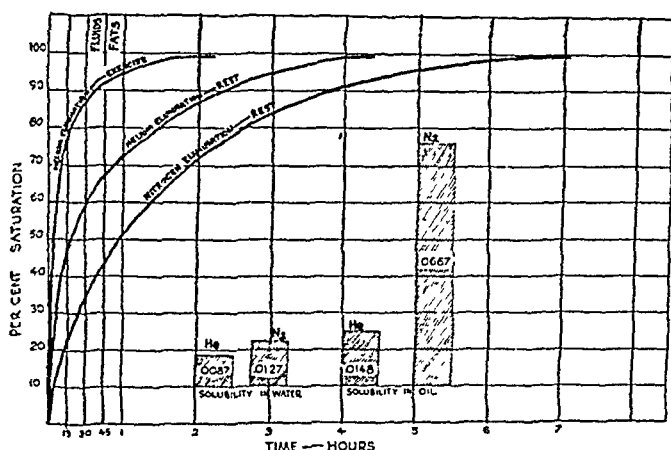


FIG. 13. Desaturation rate for man, comparing nitrogen with helium. During the first 45 minutes, gaseous removal takes place from the body fluids, and subsequently from the body fat. The solubility coefficients for helium and nitrogen are expressed as cubic centimeters of gas, reduced to standard conditions, dissolved per cubic centimeter of solvent, temperature 38° C. (From Behnke, The Harvey Lecture Series XXXVII, 1941-42.)

moreover, that two, rather than three exponential expressions required for the nitrogen curve, serve to predict accurately the curve of helium removal. In fact, the lowered oil-to-water solubility ratio and the more rapid rate of diffusion make it appear as though the helium were eliminated from one homogeneous solvent, the rôle of fat being obscured.

The reality of these considerations is apparent from table 4. Decompression following short exposures in a helium-oxygen atmosphere is actually longer than that required for air. Following saturation exposures, however, decompression time is increased from 50 to 638 minutes for air, and by contrast from 75 to 79 minutes for helium.

Absorption of radioactive krypton.—Dr. John Lawrence and Dr. Hardin Jones of the Donner Laboratory, University of California, have devised a technic of high precision for the measurement of the rate of absorption or elimination of a radioactive gas. If radio-krypton, for example, is inhaled, then a unit

of the Geiger counter held in the hand, shielded to protect against emanation from other parts of the body, will provide minute readings indicative of the rate of gaseous uptake.

The absorption curve obtained during a period of 30 minutes is similar to that characteristic of nitrogen or helium. Its value lies in its reproducibility and the frequency and accuracy of individual readings. Thus, three readings taken at 5, 10 and 20 minute intervals provide Q and k values for the exponential equation (1) that permit the calculation of intermediate values with a high degree of precision. Geiger counts recorded on an individual 5 and 10 minutes after the start of inhalation of krypton were 82 and 140, respectively (17). With these values, Q is found to be 280 and, if t is expressed in minutes, the value of k is 0.07. Substituting these values of Q and k in the equations (1), (2) and (3), the amount of gas absorbed can be computed for each minute of a

TABLE 4

Comparison of Total Decompression Time Following Exposure in Compressed Air and Exposure in a Helium-Oxygen Atmosphere

DEPTH	EXPOSURE	DECOMPRESSION*	
		Air	Helium Oxygen
<i>feet</i>	<i>minutes</i>		
90	100	50	75
90	180	—	77
90	360	—	79
90	540	638	79
150	80	141	121
150	180	—	126
150	360	—	128
200	65	217	164
200	90	—	164

* Time in minutes.

period up to about 13 minutes (table 5). Thus the calculated value for the third minute, for example, was 52 and the experimental value 56.

Likewise, the values obtained experimentally for 10 and 20 minutes can be substituted in the equations (1), (2) and (3) to provide a second set of Q and k values that enable us to compute accurately the individual minute values for gas absorbed between 13 and 25 minutes.

The k values thus obtained for the two periods of gas absorption are reproducible within a narrow range (table 6). An appreciation of the accuracy of Lawrence's technic is afforded by the consideration that to obtain k values that vary less than 0.02 units requires experimental data that agree within 1 to 2 per cent. Such accuracy is attained at times, but not consistently, for nitrogen elimination from the body as a whole (table 6).

Inhalation of radioactive gas following the occlusion test.—If the blood supply to the hand and arm be occluded for a period of 10 minutes, the inhalation of

TABLE 5
Values Showing the Absorption of Radioactive Krypton

NORMAL ABSORPTION				ABSORPTION FOLLOWING CONCLUSION		
Time	Observed Count	From Graph*	Computed Count	Observed Count	From Graph*	Computed Count
<i>min.</i>						
1	6	18	19	41	56	52
2	26	36	37	114	103	94
3	56	50	52	130	134	127
4	59	67	68	144	158	155
5	83	82	82†	173	178†	178
6	92	97	96	202	193	194
7	124	107	108	203	205	210
8	110	120	120	220	218	222
9	140	131	130	220	229	232
10	148	140	140†	232	240†	240

* The graph was a freehand fit of experimental values.

† Values employed to compute Q and k in the equation $Y = Q(1 - e^{-kt})$.

TABLE 6
Reproducibility of k Values based on Absorption of Radioactive Krypton and Elimination of Nitrogen*

SUBJECT	RADIOACTIVE KRYPTON ABSORPTION		NITROGEN ELIMINATION
	k 0-10 min.	k 10-20 min.	k 10-20 min.
SHA	.138	.103	.044
	.125	.089	.064
FOR	.130	.095	
	.114	.089	
COB	.092	.087	.079
	.110	.067	.036
FRY	.120	.073	
	.094	.069	
BEH	.106	.074	.055
	.100	.077	.064
			.040
			.040
WEL	.087	.074	
	.087	.076	
SNI	.069	.063	.064
	.066	.072	.059
MOR	.071	.063	.043
	.058	.052	.086
	.050	.059	

* $Y = Q(1 - e^{-kt})$.

krypton either at the start of, or following, the occlusive period, permits a partial analysis of some of the factors involved in gaseous saturation of the hand. The principal determinants appear to be:

- (a) absorption of gas in the lungs,
- (b) cardiac output and the transport of gas from the pulmonary bed to peripheral tissues,

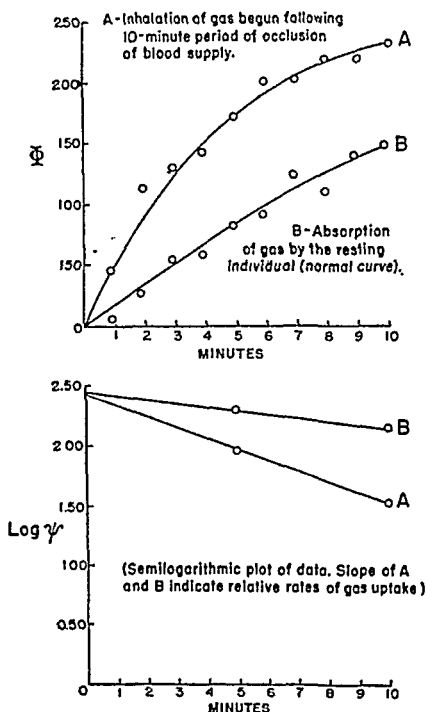


FIG. 14. Absorption of radioactive krypton by the hand
(Analysis of unpublished data of Smith.)

- (c) composition of tissues especially in relation to fat content, and
- (d) the effectiveness of peripheral blood flow in carrying gas to the greatest number of capillaries.

In figure 14, the rate of saturation depicted by the upper Curve A (following the release of occlusion) is nearly three times that shown by the lower or normal Curve B. It would appear that factor (a), in healthy subjects, would be the least variable. During the 10-minute period in which the blood supply to the

arm was cut off, on the assumption that the distribution coefficient for krypton is of the same order as that for nitrogen, equilibrium in pulmonary gaseous exchange will have taken place. Moreover, the tissues of the shoulder and arm above the restriction will have approached half saturation with respect to the absorbed gas.

In view of the maintenance of the resting state, factor (b), which involves cardiac output and some diffusion of gas through walls of large arteries, should not be greatly altered.

Factor (c) relating to tissue composition remains, of course, constant.

The most influential factor accounting for the difference in rates as shown in Curves A and B, appears to be factor (d), or effectiveness of peripheral blood flow.

Following the return of blood supply to the arm it may be assumed that large capillary beds, quiescent in the normal experiment, open up so that the transported gas is absorbed with avidity.

The actual diffusion or passage of gas through the capillary wall and into the extra- and intracellular fluids and fat, is expected to remain unchanged in both experiments A and B.

The difference in saturation rates according to Curves A and B, or between the quiescent and active capillary beds, may prove to be least in men possessing the most effective peripheral blood flow tested under basal conditions. We appear to have a measure of degree of reactive hyperemia.

The application of these studies of gaseous absorption and elimination should give additional information of cardiac output, of blood flow to the skin, of the distribution and quantitative uptake of anesthetic gases. In the perspicacious analyses of Smith and Morales (18), some rather remarkable quantitative formulations are being made relating the k 's theoretically to arterial concentration, cardiac delivery, blood volume, and the volume, permeability, vascularity, and partition coefficient of each tissue.

SUMMARY

The concept of a lean body mass of relatively constant composition in species as different as man and the guinea pig is in accord with the finding of Hastings that tissue free of fat yields closely reproducible and uniform results on chemical analysis.

That big men may or may not be "overweight" follows as a correlary of these studies. On the basis of the standard height-weight tables, 17 out of 25 professional athletes studied could be considered as not physically qualified for military duty or as first class insurance risks if an allowance of 15 per cent above the average values in the tables is considered as the upper limit. Of the 17 "All-American" football players mentioned previously, 11 fall into the group possessing high corporeal specific gravity. According to our classification, these 11 men are in prime physical condition if the absence of excessive fat is a criterion of fitness, yet the type of physical exertion engaged in by these men is proof of sturdy physique in terms of speed, agility and endurance.

We have indicated that low specific gravity is associated with adiposity and that fat deposits act as a gaseous reservoir which predisposes to bubble formation. Thus we can conclude that the "fat" man is a dangerous risk in deep sea diving but there is no doubt that he is a good candidate for survival on the life raft since he carries his emergency food supply on his person.

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DECOMPRESSION SICKNESS INCIDENT TO DEEP SEA DIVING AND HIGH ALTITUDE ASCENT^{1,2}

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In the previous lecture the concept that the body consists of a lean mass of tissue of constant composition and, in addition, variable amounts of fat, was supported by data based on determinations of specific gravity in man and the guinea pig. With respect to inert gaseous exchange, fat appears to be of great importance because of its remarkable capacity to act as a gaseous reservoir.

In this lecture we shall consider the effects in the fluid-fat mass of the wide variations in barometric pressure associated with deep sea diving and high altitude flight. A study of these pressure alterations requires the broad distinction between the manifestations of the pressure force itself which, under certain conditions, acts to distort the shape of the body mass, and those disturbances which are associated with the movement of gases into, and from, the tissues of the body.

EFFECTS OF DECOMPRESSION

Effects of compression applied equally to all parts of the body.—It is a remarkable phenomenon that the body can be compressed by 16 atmospheres (equivalent to a diving depth of 500 feet) without demonstrable change attributable to the compression itself provided that air has free access to all surfaces of the body, e.g., the membranous linings of the frontal sinuses, the ethmoid and mastoid air cells. Although the absolute cerebrospinal fluid and blood pressures are increased by 16 atmospheres, the relative pressure readings are not altered by as much as 1 mm. Hg. In so far as the pressure force operates, the brain is not in a "closed box" but is subject to the same compressive force as is the skin. That considerable pressure, in fact up to hundreds of atmospheres, is well tolerated by protoplasm has been shown by McKeen Cattell. Similarly, a decrease in ambient air pressure, corresponding to altitude ascent to 50,000 feet (equivalent to 0.11 atmospheres) will not, in itself, cause injury. This tolerance implies equal distribution of pressure to preserve unaltered the structure of tissues and the body as a whole.

Effect of unequal pressure application.—If, for any reason, the pressure is not equally distributed upon all the body surfaces, even a pressure difference amounting to no more than one-sixteenth of an atmosphere or less than 50 mm. Hg (1 pound/sq. in.) will alter the shape of tissue to induce congestion, edema, hemorrhage, and pain.

The effect of compression and differences in pressure within the body is

¹ Lecture II of The John Wyckoff Lectures on "The Composition of the Body in Relation to Decompression Sickness," delivered at New York University, 7 and 8 December 1944.

² (The contents of this lecture are not to be construed as an official expression of the views of the Navy Department.)

illustrated by the native pearl diver who, in the course of diving, is subjected to an additional compressive force of 1 atmosphere for every 33 feet of descent. At a depth of 100 feet, for example, the total pressure acting on his body is of the order of 4 atmospheres. At this depth, the air in the diver's chest at the surface, let us say 6000 cc., is compressed to one-fourth, or 1500 cc. This amount approximates the residual air volume. The depth, therefore, to which the unprotected diver descends is limited by the ratio of chest volume to residual air volume.

Should the diver now descend further, the additional hydrostatic pressure, unable to compress the rib cage without injury will bring about a condition known as a "squeeze." The effect of the "squeeze" is to force blood and tissue fluid into the respiratory passages where the residual pulmonary air is under less pressure than the tissues due to the limitation afforded by the ribs. Equalization of pressure tends to be restored by the accumulating transudate but it is at the cost of tissue trauma.

Effect of pressure differences on ears and sinuses.—In a similar manner, aural and sinal membranes are injured by a "squeeze" if the corresponding ostia of the lined spaces do not permit the free ingress of air.

During the past 12 years, thousands of our submarine personnel have been subjected to 50 pounds per square inch gauge pressure in naval recompression chambers in connection with the submarine escape drill. From 5 to 25 per cent of the trainees, at any given time, have been unable to accommodate readily the excess pressure because of "colds" or varying degrees of infection of the upper part of the respiratory tract resulting in the sealing off of the openings of the auditory tubes, and, less frequently, the sinal meatus.

In aviation during descent from altitude, the increased pressure similarly affects individuals to create a condition termed "aero-otitis media" by Armstrong and Heim (1). In civilian aviation, the stipulation that passenger aircraft must descend at a rate not greater than 300 feet per minute was based upon the difficulty generally experienced in accommodating the increased pressure. The prevalence of obstruction of the Eustachian tubes of apparently healthy individuals is indicated by an incidence of 10 per cent failure at any given time to accommodate rapidly to pressure changes. About 1.5 per cent are affected by obstruction of sinuses, and another 1.5 per cent are subject to pain in one or more teeth. The pain elicited by the unequalized pressure is confined to the area affected. The involvement of a tooth suggests the presence of a small gas pocket in the pulp or in a part of the tooth where soft tissue can be "squeezed." With reference to the ear, the pain may be felt over the mastoid area as well as in the auditory canal indicating that the entire membranous lining of the air spaces and cells is involved.

In clinical practice, a form of catarrhal otitis media and the frontal "vacuum" headache simulate closely the type of trauma ascribed to negative pressure. The occlusion of an auditory tube or frontal sinus leads to a partial absorption of oxygen proportional to the difference between the pressure in the air of 159 mm. Hg and the pressure in the lining membrane of less than 40 mm. Hg. Such

disturbance gives rise to the type of pain and the pathologic picture described for the acute injury observed in the pressure chamber.

It is recognized that, in children and infants, the presence of adenoid tissue around the opening of the auditory tube may be responsible for the frequent occurrence of catarrhal otitis media during inflammation of the nasopharynx. That the concomitant pain may be referred to the mastoid area which is tender to palpation indicates not necessarily an infective process, but a pressure trauma brought about by the rather complete absorption of the incarcerated oxygen (2).

Effect on hearing.—Following acute trauma, the audiogram reflects diminished perception of sound over the whole frequency range. As the pathologic disturbance undergoes resolution, however, hearing returns to the initial level of acuity. The rarity or absence of proved cases of deafness arising from injury incident to pressure trauma stands in contrast to the permanent aural damage caused by gunfire. Complications of suppurative otitis media, moreover, are infrequent if the traumatized tissues do not come in contact with water. The spread of infection from the nasopharynx by air passing into the Eustachian tubes during compression is not established.

EFFECTS OF DECOMPRESSION

Overdistension of the lungs.—To escape from a sunken submarine, an individual may breathe compressed air or oxygen by means of a rebreathing bag such as the Momsen lung (fig. 1). The speed of his ascent can be regulated by means of a buoy line previously released from the submarine. In this manner ascents have been made routinely in submarine escape training tanks from depths of 100 feet and in the open sea from depths of 200 feet (3).

During such ascents, the compressed gas in the lungs and in the breathing bag escapes through a relief flutter valve located on the bottom of the breathing appliance. In this manner, the intrapulmonic pressure closely approximates the ambient hydrostatic pressure.

If the individual, instead of breathing freely, holds his breath and ascends to the surface, the intrapulmonic pressure becomes higher than the hydrostatic pressure and the difference in pressure overdistends the lungs, ruptures blood vessels and gas is forced or aspirated into the blood stream. The gas emboli subsequently produce symptoms referable to the central nervous system and the circulation. The following description of symptoms produced by too rapid ascent combined with breath holding is typical:

"About a minute later he slowly collapsed in the water. The extremities and body were cold and the muscles were rigid. Breathing was shallow and rapid and the pupils were dilated, but reacted to light. The radial pulse was absent and the heart seemed slow and weakened. After about 15 minutes, the patient began to make sounds and to roll his eyes about. He was then dressed, but gave no assistance to this act and made thrashing, and apparently hysterical movements with the arms and legs. When seen about a half hour later, he complained of loss of vision, even to light, and anesthesia of the left foot and leg."

If, in tests, one purposely holds his breath during ascent, a sensation of substernal distress and a feeling of actual stretching of the lungs forces exhalation.

illustrated by the native pearl diver who, in the course of diving, is subjected to an additional compressive force of 1 atmosphere for every 33 feet of descent. At a depth of 100 feet, for example, the total pressure acting on his body is of the order of 4 atmospheres. At this depth, the air in the diver's chest at the surface, let us say 6000 cc., is compressed to one-fourth, or 1500 cc. This amount approximates the residual air volume. The depth, therefore, to which the unprotected diver descends is limited by the ratio of chest volume to residual air volume.

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During the past 12 years, thousands of our submarine personnel have been subjected to 50 pounds per square inch gauge pressure in naval recompression chambers in connection with the submarine escape drill. From 5 to 25 per cent of the trainees, at any given time, have been unable to accommodate readily the excess pressure because of "colds" or varying degrees of infection of the upper part of the respiratory tract resulting in the sealing off of the openings of the auditory tubes, and, less frequently, the sinal meatus.

In aviation during descent from altitude, the increased pressure similarly affects individuals to create a condition termed "aero-otitis media" by Armstrong and Heim (1). In civilian aviation, the stipulation that passenger aircraft must descend at a rate not greater than 300 feet per minute was based upon the difficulty generally experienced in accommodating the increased pressure. The prevalence of obstruction of the Eustachian tubes of apparently healthy individuals is indicated by an incidence of 10 per cent failure at any given time to accommodate rapidly to pressure changes. About 1.5 per cent are affected by obstruction of sinuses, and another 1.5 per cent are subject to pain in one or more teeth. The pain elicited by the unequalized pressure is confined to the area affected. The involvement of a tooth suggests the presence of a small gas pocket in the pulp or in a part of the tooth where soft tissue can be "squeezed." With reference to the ear, the pain may be felt over the mastoid area as well as in the auditory canal indicating that the entire membranous lining of the air spaces and cells is involved.

In clinical practice, a form of catarrhal otitis media and the frontal "vacuum" headache simulate closely the type of trauma ascribed to negative pressure. The occlusion of an auditory tube or frontal sinus leads to a partial absorption of oxygen proportional to the difference between the pressure in the air of 159 mm. Hg and the pressure in the lining membrane of less than 40 mm. Hg. Such

disturbance gives rise to the type of pain and the pathologic picture described for the acute injury observed in the pressure chamber.

It is recognized that, in children and infants, the presence of adenoid tissue around the opening of the auditory tube may be responsible for the frequent occurrence of catarrhal otitis media during inflammation of the nasopharynx. That the concomitant pain may be referred to the mastoid area which is tender to palpation indicates not necessarily an infective process, but a pressure trauma brought about by the rather complete absorption of the incarcerated oxygen (2).

Effect on hearing.—Following acute trauma, the audiogram reflects diminished perception of sound over the whole frequency range. As the pathologic disturbance undergoes resolution, however, hearing returns to the initial level of acuity. The rarity or absence of proved cases of deafness arising from injury incident to pressure trauma stands in contrast to the permanent aural damage caused by gunfire. Complications of suppurative otitis media, moreover, are infrequent if the traumatized tissues do not come in contact with water. The spread of infection from the nasopharynx by air passing into the Eustachian tubes during compression is not established.

EFFECTS OF DECOMPRESSION

Overdistension of the lungs.—To escape from a sunken submarine, an individual may breathe compressed air or oxygen by means of a rebreathing bag such as the Momsen lung (fig. 1). The speed of his ascent can be regulated by means of a buoy line previously released from the submarine. In this manner ascents have been made routinely in submarine escape training tanks from depths of 100 feet and in the open sea from depths of 200 feet (3).

During such ascents, the compressed gas in the lungs and in the breathing bag escapes through a relief flutter valve located on the bottom of the breathing appliance. In this manner, the intrapulmonic pressure closely approximates the ambient hydrostatic pressure.

If the individual, instead of breathing freely, holds his breath and ascends to the surface, the intrapulmonic pressure becomes higher than the hydrostatic pressure and the difference in pressure overdistends the lungs, ruptures blood vessels and gas is forced or aspirated into the blood stream. The gas emboli subsequently produce symptoms referable to the central nervous system and the circulation. The following description of symptoms produced by too rapid ascent combined with breath holding is typical:

"About a minute later he slowly collapsed in the water. The extremities and body were cold and the muscles were rigid. Breathing was shallow and rapid and the pupils were dilated, but reacted to light. The radial pulse was absent and the heart seemed slow and weakened. After about 15 minutes, the patient began to make sounds and to roll his arms about. He was then dressed, but gave no assistance to this act and made shivering and apparently hysterical movements with the arms and legs. When seen about a half hour later, he complained of loss of vision, even to light, and anesthesia of the left foot and leg."

If, in tests, one purposely holds his breath during ascent, a sensation of substernal distress and a feeling of actual stretching of the lungs from within

tion at periodic intervals. A condition of fright, however, can apparently cause a spasm of the glottis to seal the trachea to bring about overdistension of the lungs. Under this circumstance death has occurred in ascent from depths of only 15 feet. On the other hand, without any escape appliance, ascents can be made from depths of 100 feet provided the individual exhales periodically.

Spontaneous pneumothorax.—Either with or without air embolism during rapid decompression, spontaneous pneumothorax may occur in the distended lung. The following description of an accident in submarine escape training illustrates this complication:

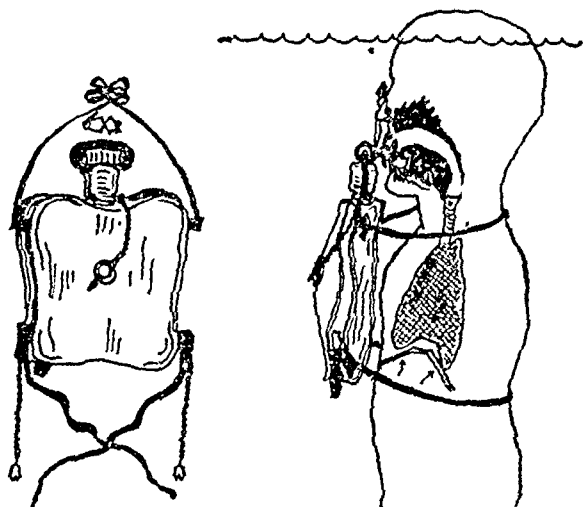


FIG. 1. The individual submarine escape appliance. The distance of the relief flutter valve on the bottom of the bag determines the static breathing pressures in the bag and the lungs.

An individual "blew-up" from a depth of 20 feet in the submarine escape training tank. Examination revealed loss of consciousness, stertorous, gasping respiration, blood froth on the lips, and dilated pupils with fixation of eyes to the left. During recompression consciousness was regained at a simulated depth of 15 feet and the patient felt all right at 50 feet. Following this treatment the patient complained of substernal soreness and was again compressed in the chamber to a simulated depth of 100 feet. He strained considerably during the compression in order to "clear" his ears.

Upon decompression at the 40-foot level, a pneumothorax was found present on the left side. At the 20-foot level the patient was dyspneic, cyanotic and excited. The pulse was erratic and weak, respirations were rapid and shallow. Oxygen was administered intermittently with some relief for a period of 20 hours. It was necessary, however, at the 10-foot level to remove 1500 cc. of air from the thoracic space on the left side and an additional 750 cc. of air before the ambient pressure could be reduced to normal barometric pressure. Resolution of the pneumothorax occurred during the next few days.

It appears likely that the pneumothorax occurred primarily as a result of previous overdistention of the lungs during the second decompression and was precipitated by the patient's straining to "clear" his ears.

The mechanism of this type of spontaneous pneumothorax developing incident to changes in barometric pressure has been studied by Gersh (4) who observed atelectatic lungs in 7 out of 400 cats subjected to, and subsequently decompressed rapidly from, high pressure oxygen atmospheres. The primary defect appeared to be a rupture of a few alveoli with passage of gas beneath the visceral pleura to the mediastinum and subsequent rupture of mediastinal pleura to permit the entrance of gas into the thoracic space during decompression. In man some confirmatory evidence in support of this mechanism has been obtained at autopsy in the rare fatal accident in connection with submarine escape training.

Overdistension of abdominal viscera.—In ascent from deep diving depths, and more frequently in ascent to high altitudes, the expansion of gas trapped in the stomach and segments of the large bowel constitutes a serious impediment to further decompression. A viscous once having been distended with gas loses much of its functional motility. In distension of the stomach, for example, the cardiac and pyloric sphincters remain so tightly contracted that rupture of the gastric wall may take place.

PRESSURE CHANGES IN RELATION TO GASEOUS EQUILIBRIA

Narcotic action of nitrogen.—The phenomena described have arisen primarily from differences in pressure which have acted to distend and rupture blood vessels and membranes. On a wholly different basis are those pressure phenomena associated with disturbances in gaseous equilibria.

When the air pressure is raised to 4 atmospheres or higher, the gaseous nitrogen induces a narcotic action manifest by decreased ability to work and changes in mood which may be no more than mild euphoria (5) (6). A slowing up of mental activity and fixation of ideas are characteristic responses. Recollection requires greater effort and concentration is difficult. Frequent errors may be made in arithmetical calculation and in the recording of data. The responses necessary for proper motor performance and accuracy are impaired. The responses may, in fact, be indistinguishable from those associated with anoxia or alcoholic intoxication. Although all individuals are to some extent narcotized at deep diving depths, stable individuals react to the stress by increased effort and carry out their tasks until consciousness is lost. The unstable individual, on the other hand, is incapable of purposeful effort and is apt to dissipate his energies through vocal, pugilistic or narrative channels.

The substitution of a helium-oxygen atmosphere for air minimizes or abolishes the untoward reactions and the previously abnormal individual becomes an efficient worker.

Why helium, in contrast to nitrogen, is not narcotic is not entirely clear. The physical properties of the gas may be of great importance since argon, although chemically inert like helium, nonetheless elicits the nitrogen type of narcosis. The oil-water solubility ratio and the molecular weight may be important. In accord with the Meyer-Overton concept is the fact that helium possesses an oil-water solubility ratio one-third that of either nitrogen or argon. Furthermore, the molecular weight is only one-seventh that of nitrogen. Whatever the physiologic basis of action, the intriguing fact is that atmospheric

nitrogen, an elementary and inert gas as it exists in the body at normal pressure, will induce a narcotic type of unconsciousness under high pressure.

Decompression sickness.—The more familiar phenomenon relative to exposure to variations in atmospheric pressures is the formation of gas bubbles in the blood stream and tissues following too rapid decompression. Robert Boyle, in 1670, with discerning prescience, outlined what appears to be the true nature of compressed air illness in the following statements quoted from the paper of Professor John Fulton (7):

"The little Bubbles generated upon the absence of the Air in the Bloud, juyces, and soft parts of the Body, may be their Vast number, and their conspiring distention, variously streighten in some places, and stretch in others, the Vessels, especially the smaller ones, that convey the Bloud and Nourishment; and so by choaking up some passages, and vitiating the figure of others, disturbe or hinder the due circulation of the Bloud!"

Paul Bert, in 1878, exemplifying the perspicacity that distinguished the brilliant French scientists, presented experimental proof of the relationship between air embolism and decompression symptoms in his classic book, "*L'apression Barometrique*" (8). The use of recompression as the proper treatment for compressed air illness is but the application of Paul Bert's theory. No therapeutic procedure is more effective than recompression. It is the specific treatment of the asphyxiated, pulseless, cyanotic patient whose blood stream is filled with multiple gas emboli.

The fluid-fat mass subjected to increased pressure, doubles its nitrogen content for each atmosphere of increased pressure provided that the exposure is sufficiently prolonged. If decompression is properly regulated, the transport agent, blood, carries the excess nitrogen in physical solution to the lungs. Too rapid decompression, however, produces bubbles in the blood stream and in fatty tissue.

Macro- and microscopic observations.—In dogs rapidly decompressed from high atmospheric pressure (60 pounds gauge), small bubbles can be observed first circulating rapidly through cutaneous arteries and veins and later bubbles of gradually increasing size are found to slow down and eventually stop circulation (9).

In monkeys fitted with leucite calvaria, according to the method of Sheldon and Pudenz (10), the formation and movement of bubbles in the cerebral blood vessels can be observed following rapid decompression.

Wagner (11) at the Naval Medical Research Institute has observed through a Forbes window the movement of gas bubbles in the pial blood vessels of cats. The bubbles always appeared first in the arteries, and later, as the blood flow decreased, in the veins. Sludge formation, or the close grouping in compact masses of red blood cells separated by zones of clear plasma, accompanied the reduction in blood flow. This clumping of cells described previously by Swindle (12) is not a true agglutination but a phenomenon that occurs as Knisely has demonstrated under a variety of conditions associated with slowed circulation, plasma loss and cell packing.

In the histologic studies of Gersh (13) on rapidly decompressed guinea pigs, intravascular gas bubbles occurred in all tissues and organs but were far more

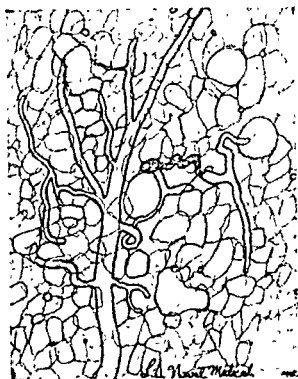


FIG. 2



FIG. 3

FIG. 2. Camera lucida drawing of a portion of a section of fat showing a terminal venule and venous capillaries greatly distended with gas. Also represented is an arteriole (stippled) which contained red blood cells in one portion and which in another portion is markedly stretched and thinned. Tissue was taken from a guinea pig which had been rapidly decompressed from a high pressure atmosphere (from Gersh and Hawkinson, Research Project X-284, Report No. 1, Naval Medical Research Institute).

FIG. 3. Photomicrographs of sections of the adrenal gland of a guinea pig decompressed from high pressure (after Gersh and Hawkinson, Research Project X-284, Report No. 1, Naval Medical Research Institute).

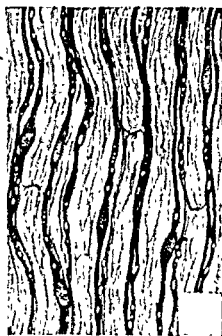


FIG. 4. Idealized drawing of minute bubbles in myelin sheath of nerve fibers from section of sciatic nerve. Tissue was taken from a guinea pig killed 5 seconds after decompression (Gersh and Hawkinson, Research Project X-284, Report No. 1, Naval Medical Research Institute).

numerous in those rich in fat. Extravascular bubbles were observed only in tissue rich in fat and in the lipid matter of the adrenal cortex and the myelin sheaths of nerve fibers (figs. 2, 3, and 4).

From figure 5 the successive stages of bubble formation observed in fat tissue by Gersh are (1) enlargement of fat cells by inclusions of minute bubbles (B and C), (2) rupture of gas filled cells to produce pockets (D), and (3) rupture

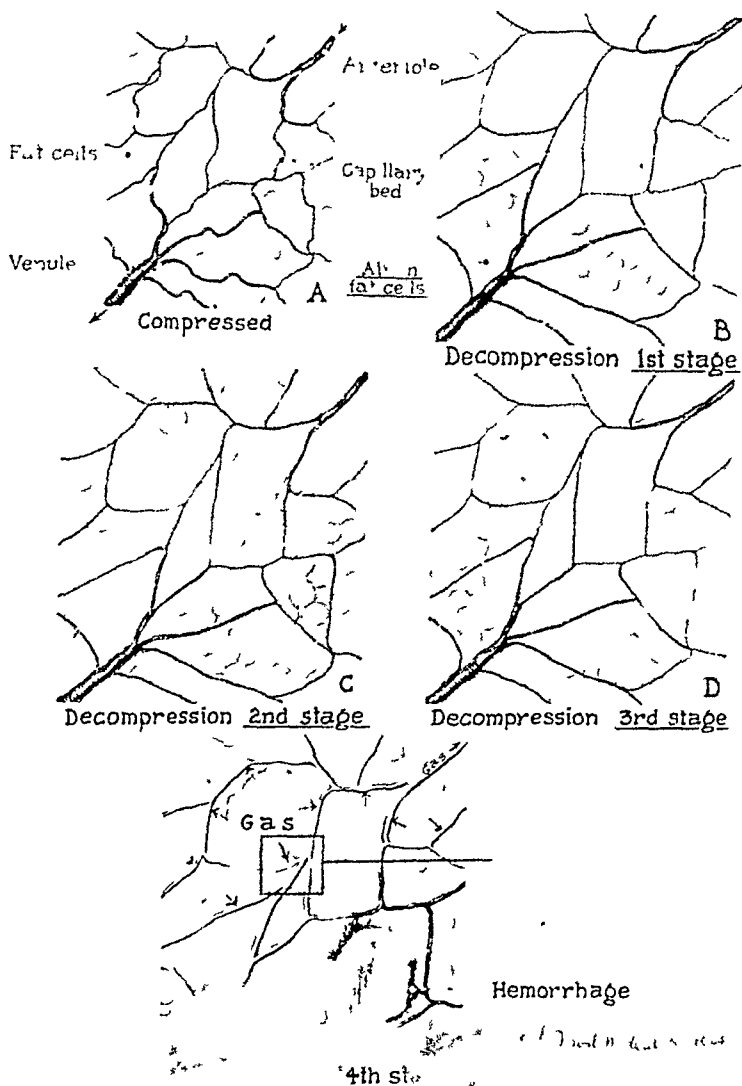


FIG 5. Stages of bubble formation from high pressure atmosphere.

As the fat tissue is decompressed, the enlargement of the fat cells and the rupture of gas-filled cells and vessels to produce pockets of gas (Hawkins, 1951).

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Of considerable importance are the observations that bubbles may be present in the blood vessels and not extravascularly in fat, and that fat guinea pigs in comparison with lean animals not only show extensive intra- and extravascular bubble formation but that these bubbles form in the fat guinea pigs at considerably lower decompression levels.

That bubbles pass from gas pockets in fat into the blood stream has not been demonstrated but it would be possible for such tissue bubbles to enter ruptured vessels. The capacity of fat, however, to act as a gaseous reservoir is certain from these histologic studies.

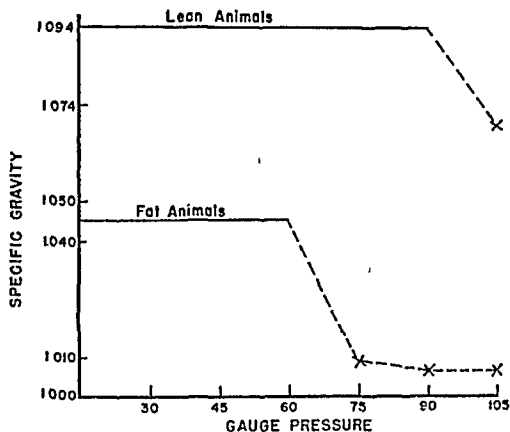


FIG. 6. Relationship of specific gravity of the guinea pig to gauge pressure following decompression in 4 seconds after 1-hour exposures in compressed air (after Gersh, Hawkins, Rathbun and Behnke, Research Project X-284, Report No. 2, Naval Medical Research Institute).

Quantitative evaluation of bubble formation.—If the specific gravities of the bodies as a whole of guinea pigs and of individual tissues are measured and compared before and after rapid decompression, a measure of the degree of intravascular and extravascular bubble formation is afforded (14). When guinea pigs were decompressed from pressures of less than 45 pounds per square inch, there was no change in specific gravity of either the animal as a whole or the fatty tissues. Decompression in 4 seconds, however, from pressure levels of from 60 to 105 pounds per square inch was associated with a linear decrease in specific gravity (fig. 6). Fat tissue itself varied from 0.95 to 0.65, adrenal gland from 1.045 to 0.97, and the guinea pig as a whole from 1.050 to 1.00, when gas bubbles were present in tissues.

Again it is the fat guinea pig that showed the most marked decrements in specific gravity beginning at levels as low as 60 pounds per square inch. The

specific gravity values of lean guinea pigs even at the highest pressures used (105 pounds per square inch), were only slightly affected.

The influence of oil to water solubility ratio.—If now, the same procedures employed to produce bubbles in an air atmosphere are repeated using the following gas mixtures, these relationships are obtained (15):

	<i>Bubbles form following decompression from</i>
Argon-oxygen.....	60 lbs/sq. in.
Nitrogen-oxygen (air).....	75 lbs/sq. in.
Helium-oxygen.....	90 lbs/sq. in.
The highest pressures employed consistent with survival time were:	
Argon-oxygen.....	30 lbs/sq. in.
Nitrogen-oxygen (air).....	45 lbs/sq. in.
Helium-oxygen.....	75 lbs/sq. in.
Oxygen.....	90 lbs/sq. in.
	(3 out of 4 guinea pigs survived)

Symptoms in man arising from rapid decompression.—The rapid release of ambient pressure may give rise to pain, paralysis and asphyxia. Minor symptoms are pruritus, skin rash, and fatigue. That the symptoms arise primarily not from free gas in fat but from obstruction to blood flow by intravascular bubbles accumulating in peripheral and pulmonary blood vessels, especially the veins, is consistent with most of the data bearing on this type of injury.

That bubbles in subcutaneous fat tissue are not productive of pain is inferred from the following observations. If the procedure termed denitrogenation is employed for a period of one hour to remove, for the most part, the gaseous nitrogen dissolved in body fluids, then an individual may be rapidly exposed to an altitude of 46,000 feet without developing symptoms of aeroembolism. Furthermore, the subcutaneous emphysema which can be produced by the mild trauma incident to periodic inflation of a sphygmomanometer pressure cuff about the arm, does not give rise to pain and yet crepitus so produced will disappear with reapplication of ambient pressure.

Further evidence that the gas in fat does not cause symptoms consists in the observation that pain arising from too rapid decompression in helium atmospheres is similar to the pain occurring in compressed air illness. Helium, as previously pointed out, is present in rather negligible amounts in fat or diffuses rapidly out of fat, thus predisposing to bubble formation in the blood.

Bends.—The most common manifestation of compressed air illness is a dull, throbbing type of pain, gradual in onset, progressive and shifting in character, and frequently felt in the joints, or deeply in muscles and bones. Pain or pains of this nature are referred to as "bends", a term established by usage to denote a well recognized clinical entity. Prior to the onset of pain there may be, particularly in the joints, paresthesia frequently described as numbness or merely an awareness that "something is not right." Skin temperature may fall as the part involved becomes blanched in appearance.

A most likely location giving rise to bends is bone, particularly the marrow, with its high absorption coefficient for nitrogen. Furthermore, the sinusoid type of circulation in the marrow and the natural obstructions to the exit of bubbles, consisting of dichotomous branches of a vein traversing the rigid-walled cortex, serve to make the bones a trap for gas bubbles disseminated from the general circulation or forming *in situ* in the marrow spaces. From the point of view of body economy, bone is the organ that renders man unmanageable for long exposures in compressed air.

That bubbles are present in the marrow is inferred from the intensified symptoms experienced by some subjects during early recompression. This type of symptom is believed to arise from a difference in pressure, or an actual "squeeze" of the marrow tissue, resulting from compression of bubbles which is so rapid that the body fluids cannot immediately replace the suddenly diminished gas volume within the bone cortex.

Recent reports of characteristic lesions in bone (Henry Taylor, N. Y. J. (16) appearing in caisson workers support the view that the symptoms of bends arise to bends originate, in part at least, from *ischemic changes in bone*. Strom, Burton, and Phemister (17), Coley and Moore (18), and Rendic and Harrington (19) describe lesions in diaphyses and epiphyses of long bones complicated by joint involvement and attributed to aseptic necrosis of bone or interference with nutrition occurring secondary to the interruption of blood supply by liberated nitrogen gas.

However, the etiologic relationship between the presence of these lesions and embolic injury must be corroborated by additional findings and animal experiments before final conclusions can be drawn. In divers suffering repeatedly from experimental bends, Lieutenant Commander Walter Welham, USN, and the writer found no characteristic lesions in a roentgenologic examination at different periods following injury.

Some factor, such as multiple repeated injury, concomitant infection, or anomalous blood supply must operate in conjunction with embolism to produce the described changes. The analogy that may be drawn to the relationship between the ingestion of alcohol and cirrhosis of the liver suggests that an integrative analysis is required to evaluate the findings.

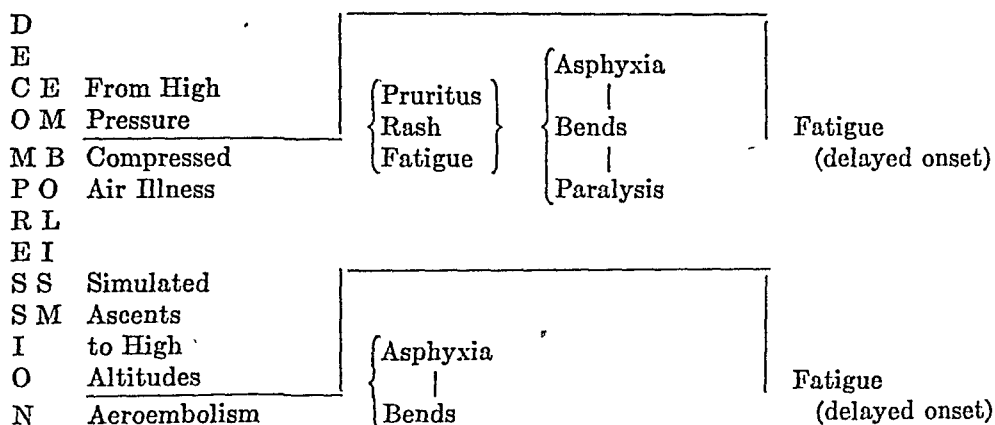
That gas emboli form to interfere with the blood supply to muscles and bone tissue is also consistent with the symptoms of bends especially those which occur in rapid decompression in a helium atmosphere. The decreased solubility of helium in fat renders the incidence of bone lesions less likely than the incidence of these lesions following air decompression. Following helium dives the upper extremities are more frequently afflicted with bends than they are following compressed air dives. Swelling of the arms is not uncommon and cramps have been elicited along the brachial veins suggesting that venous return has been partially blocked by the gas emboli. Vasoconstriction of cutaneous vessels is evident by the pallor and fall in temperature of the skin. Fatigue is a symptom of especial interest which may be prodromal or subsequent to bends. In experimental borderline decompressions, fatigue is frequently the first

of excessive bubble formation. In association with bends, fatigue may take the form of an exhausting malaise combined with chills, fever, and sweating.

Minor symptoms as *skin rash* and *pruritus* occur with regularity if the skin is chilled during decompression.

It is important to bear in mind that the *onset of symptoms* may occasionally be delayed as long as twelve hours following decompression and that sudden collapse may occur without warning in an apparently well individual three or four hours following decompression. The failure to consider these probabilities has led to errors in treatment (20).

The following diagram may clarify the symptomatology of decompression embolism:



Our deep sea divers have experienced symptoms during simulated ascents to high altitudes identical with the bends characteristic of compressed air illness as indicated in the above outline (21). Paralysis alone of the symptoms is less likely to occur at high altitude. Other disturbances attributable to injury of the nervous system, barring visual symptoms, are also rare occurrences.

On June 25, 1942 a diver breathing a helium-oxygen mixture for a period of 30 minutes at a depth of 400 feet was decompressed too rapidly. His chief complaints were pain, swelling, and limitation of motion confined to the right ankle.

On July 28, 1942 he served as a subject for rapid decompression to a simulated altitude of 38,500 feet. This test was terminated after a period of 46 minutes because of intense pain affecting the right ankle.

Paralysis.—The most serious complication of decompression sickness is paralysis. The spinal cord with its relatively poor blood supply in comparison with the brain is most frequently involved. Within the spinal cord itself, the regions frequently involved are the lower thoracic and upper lumbar portions giving rise to weakness of the lower extremities, spastic paraplegia, and genito-urinary impairment (22).

Dogs rapidly decompressed from high pressures and then only partially recompressed (to a degree that prevents death from asphyxia) frequently develop paralysis of the hind legs, foot drop, a spastic type of gait, and paralysis of the bladder musculature.

Similar symptoms in man are usually followed by gradual remission. For an individual following decompression to remain in apparently good condition for a period of several hours and then collapse because of paralysis of the lower extremities is characteristic of the insidious nature of the injury. Fortunately, immediate and prolonged recompression usually brings about immediate recovery even following paraplegia of the lower extremities.

In the dog and in man incompletely treated by recompression following massive embolism, residual symptoms may persist for months.

There is a remarkable lack of cerebral involvement even under conditions of widespread embolism. Vertigo, deafness, occasional aphasia, and transient visual disturbances have been recorded. In contrast with spinal cord lesions, permanent impairment referable to lesions of the brain is rare.

Clinical conditions manifesting symptoms similar to those associated with the presence of air emboli in the spinal cord are tabes dorsalis, and arteriosclerosis of the terminal aorta involving the lumbar segmental arteries. Reichert et al. described the conditions of four patients who exhibited weakness of the thighs on exertion, not accompanied by pain and associated with normal pulsation of the femoral arteries. These patients showed, however, extensive calcification of the terminal aorta. Reichert confirmed his observations by producing a similar syndrome in dogs following ligation of the lumbar segmental arteries. (23).

The effect of interference with the blood supply to tissues by intravascular bubble formation in young, healthy, vigorous men simulates the symptoms associated with the aged or with individuals afflicted with arteriosclerosis or syphilitic arterial disease. Fortunately, incipient lesions incident to ischemia induced by gas emboli undergo rapid resolution if blood flow is promptly restored by the application of adequate recompression.

"Chokes".—The most interesting manifestation of decompression sickness is a type of asphyxia designated most aptly by the early caisson workers as "chokes". In comparison with bends, chokes occur less frequently since they apparently require the accumulation of quantities of gas eliminated from the arterial circulation and extravascular tissues into the large veins, the right side of the heart and pulmonary vessels.

Thus, several hours of complete well being following decompression may elapse before the appearance of the earliest symptom of chokes, namely, a sensation of substernal distress felt only during deep inspiration which frequently serves to elicit the cough reflex. This sensation of substernal distress may be only transient or it may progress to frank asphyxia. Normal breathing becomes shallow, rapid and then dyspneic. The skin becomes cyanotic, or ashen gray, cold and clammy. The pulse beat, at first slow and pounding, becomes thready. Paroxysmal attacks of coughing or true "chokes" may precede loss of consciousness. The picture presented is one of "shock" and represents a transformation within a period usually of several hours from a state of health and vigor to one of incapacitation without any apparent trauma being inflicted upon the individual. It is this condition that not only frequently supervenes in

divers when the premonitory symptoms of bends are ignored and treatment delayed but may also be responsible for circulatory collapse and deaths which occasionally occur following too rapid decompression in the low pressure chamber.

A clearer concept of the etiologic factors underlying the progression from a state of well being to shock may be derived from studies of anesthetized dogs rapidly decompressed from high atmospheric pressures.

TABLE 1

Relationship between nitrogen bubble formation, respiratory rate and blood pressure in dogs rapidly decompressed from high atmospheric pressures

EX- PERI- MENT NO.			REMARKS
2	Time* Resp. rate Blood pres.	12 36 20 20 110 110	Compression 45 lbs/sq. in. for 4 hours followed by decomp. Dog in good condition the following day.
4A	Time* Resp. rate Blood pres.	4 8 14 17 21 25 94 200 24 22 34 24 50 54 36 19 (Values remained between 120-130 mm. Hg)	Compression 60 lbs/sq. in. for 1.5 hours
4B	Time* Resp. rate Blood pres.	3 7 25 33 37 45 46 14 14 9 8 7 7 Failure 124 120 140 60 40	Compression 60 lbs/sq. in. for 2 hours followed 200 min. after initial compres. (4A).
6A	Time* Resp. rate Blood pres.	3 11 14 27 19 21 26 32 36 58 7 19 20 38 69 78 92 47 17 11 90 112 90 90	Compression 60 lbs/sq. in. 2 hours
6B	Time* Resp. rate Blood pres.	1 3 Recompression 9 Failure 64 110 to 25 120 92 88	Compression 75lbs/sq. in. for .55 hour followed 58 min. after initial compres. (6A)

* Minutes following decompression.

Anesthetized dogs in complete equilibrium (100 per cent saturation) with the partial pressure of nitrogen in air at 45 pounds gauge pressure can be decompressed in 10 seconds to atmospheric pressure without disturbances of respiration or blood pressure, indicating that either nitrogen bubbles have not formed in the blood, or that they are not of sufficient size and number to cause symptoms. That bubbles can exist in the blood stream without producing symptoms is proved by numerous experiments in which small quantities of air have been introduced intravenously without harmful effects.

Decompression in 10 seconds, however, from 60 pounds gauge pressure after 1.5 hours exposure, after an interval of about one-half hour, may be associated with a moderate increase in respiratory rate (table 1, experiment 4A). The return of breathing to the initial rate indicated that the degree of bubble formation was within the dogs' range of tolerance and the gas in bubble form was eliminated in the lungs. At the same time that rapid breathing begins, bubbles may be seen moving through cutaneous arteries and veins. A second exposure, however, of 2 hours duration followed by rapid decompression results in bubble formation of sufficient magnitude to fill the right ventricle and pulmonary blood vessels, thereby bringing about immediate asphyxial death. This acute asphyxia is not preceded by tachypnea (table 1, experiment 4B). An asphyxial rise in blood pressure to 140 mm. Hg is observed followed by a rather precipitous fall to 40 mm. Hg.

The relationship between rapid breathing and pulmonary gas embolism.—The symptoms from multiple gas emboli as produced in these experiments are remarkably similar to those associated with pulmonary embolism arising from intravenous starch injections in goats (24), and from starch or seed injection into dogs (25). Of particular interest is the mechanism underlying the production of rapid, shallow breathing. Binger and his associates were able to distinguish rapid breathing due to obstruction of the pulmonary arterioles and capillaries from that due to obstruction of the larger branches of the pulmonary artery. They concluded, with reference to the etiology of rapid breathing that obstruction of arterioles and capillaries initiated reflex stimuli, while obstruction of the pulmonary artery and its branches produced anoxemia. The reflex stimuli were thought to be the result of a particular lesion in the lungs, namely, congestion and edema which through a limitation of lung expansion probably initiated impulses through the vagal nerve endings. The mechanism underlying anoxemia was thought to be a more quickened blood flow through a diminished vascular bed resulting in a change in the quantitative relation of blood flow to the vascular diffusion area in the lungs.

The results of these experiments, in contrast with the work of Binger and his associates, do not conclusively distinguish between anoxemia and the mechanical effect of bubbles in producing rapid breathing since both factors are removed by the same treatment, i.e., bubble absorption by compression and oxygen breathing. The rapid breathing is, however, considered to result primarily from reflex stimuli arising from the mechanical action of gas bubbles in the pulmonary vessels, and from anoxemia.

Thus a respiratory rate of 90 following decompression (table 2) will return to 20 if oxygen is administered and the dog recompressed to 30 pounds gauge pressure. As the pressure is slowly reduced, the respiratory rate again increases. At atmospheric pressure, the rate rises to 40 and then to 52 if oxygen is replaced by air. The continuance of the experiment by a third period of compression reduces the rate to 22, from which, following a terminal decompression, it rises to 100.

The degree of tachypnea is of such magnitude as to indicate that reflex stimuli

arising from the mechanical action of gas bubbles in pulmonary vessels play a more important rôle than does anoxia. The failure of a high concentration of carbon dioxide in arterial blood (table 3) to change the pattern of the rapid shallow breathing is further evidence of the powerful effect of these reflex stimuli.

According to Heller, Mager, and von Schrötter (26), the effect of gas in the pulmonary vessels is to displace blood and to inflate the lungs intravascularly

TABLE 2

Relationship between respiratory rate, air pressure, and the inhalation of air and of oxygen

Experiment 9.

TIME	TREATMENT	RESP. RATE	REMARKS
12:22	65 pounds air pressure	26	105 minutes compression
12:33	Foll. decomp.	90	Period of bubble formation, air 1 atm.
1:04	Oxygen 30 lbs.	20	Recompression
1:10	Oxygen 10 lbs.	30	Oxygen decompression
1:16	Oxygen 5 lbs.	32	
1:32	Oxygen 1 atm.	40	
2:30	Air 1 atm.	52	
3:00	Oxygen 1 atm.	40	
3:09	Air	40	
3:50	65 lbs. air	22	p.p. of O ₂ 1.12 atms.
4:06	Following decomp.	100	Period of bubble formation

TABLE 3

Physiologic effects of too rapid decompression (5-6 seconds) of dogs exposed to 65 lbs. sq. in. gage pressure for a period of 105 minutes

	ARTERIAL pCO ₂	RESP. RATE	% SAT. HbO ₂	BLOOD PRES.	ARTERIAL VENOUS O ₂ DIF.	O ₂ CAPACITY
	(1)	(2)	(3)	(4)	(5)	(6)
Control Period.....	45	20	90	116	3.6	22.8
Post compression period.....	59	142	24	140 to 30	6.9	26.1
Recompression period.....	56	40	88	90	11.7	27.3
Period following recompression.....	59	125	26	100*	19.6	29.8

* Oxygen was inhaled during the 2-hour recompression period.

producing a decreased alveolar ventilation. The shallow breathing may, therefore, be tentatively looked upon as primarily the result of reflex stimuli initiated by alternate distension and contraction of gas containing vessels during inspiration and expiration respectively. Gersh has demonstrated the remarkable distortion that occurs in the gas filled pulmonary vessels of the guinea pig.

In man, limitation of deep inspiration may be considered to be a sign

pathognomonic of the presence of bubbles in pulmonary vessels. Both divers and aviators following too rapid decompression have been affected by restricted breathing. The sense of substernal irritation, tracheal dryness, and pain accompanied by coughing when deep inspiratory effort is made stands in contrast with the absence of symptoms if breathing is shallow. The disappearance of symptoms with recompression or sometimes oxygen inhalation, and the presence of pulmonary bubbles in dogs in association with rapid, shallow breathing supports the view that the substernal distress in man is caused by bubbles.

TABLE 4

Effect of recompression with air and with oxygen on the blood pressure

Period of compression 105 min. at 65 pounds gage pressure. Rate of decompression 5-6 seconds.

EXP.	BLOOD PRESSURE				
	(A) Control	(C) Asphyxial Per.		(C) Recomp. 30 lb. 1.5 hours	1 hour foll. recomp. Air 1 atm.
		High (2)	Low (3)		
11 O ₂ *	127	166	64	104	100
14 O ₂	102	110	62	74	74
15 O ₂	117	136	60	115	
20 O ₂	116	140	30	90	100
22 O ₂	150	172	68	90	80
23 O ₂	158	166	84	60	65
13 Air*	147	154	80	106	102
16 Air	97	104	62	80	85
17 Air	142	130	78	122	80
18 Air	115	128	54	100	108
19 Air	128	162	86	124	125
21 Air	132	137	80	86	114
26 Air	146	120	64	90	90

* Breathed during recompression period at 30 lbs. pressure.

In divers and aviators exposed to pressure changes the limitation of respiration serves as a premonitory sign that asphyxia and circulatory collapse may be imminent.

Changes in blood pressure and pulse rate.—During the period of tachypnea following rapid decompression both pulse rate and blood pressure fall (fig. 7). That these asphyxial phenomena are in fact reversed by recompression, which serves to compress the obstructing bubbles, is apparent.

A temporary rise in blood pressure usually preceded the precipitous fall (table 4). This rise may be due to increased peripheral resistance as a result of multiple embolism. The abrupt fall in blood pressure is certainly, in part, dependent upon impaired blood flow to the left ventricle when the pulmonary circuit becomes filled with gas. Not only is it probable that mechanical blockage of blood flow takes place in the pulmonary circuit by bubbles but the force of

contraction of the right ventricle may be dissipated in compressing gas bubbles instead of propelling a fluid column.

The frequent precipitous fall in blood pressure is abruptly checked by the reapplication of pressure (fig. 7) and a rise usually occurs, although seldom to the initial level (table 4). The incomplete recovery of blood pressure is not related to anoxemia or to the presence of bubbles since pressure combined with oxygen does not bring about an improvement. It is interesting to note that, after the period of recompression, blood pressure may be maintained at a fairly high level associated with a degree of anoxemia (oxygen saturation of the hemo-

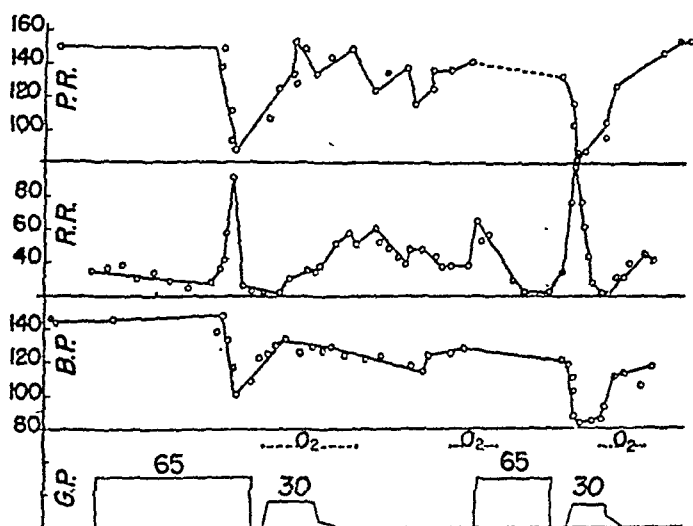


FIG. 7. Alterations in blood pressure, respiratory rate, and pulse rate of a dog decompressed in 10 seconds from a gauge pressure of 65 pounds after 1.5 hours exposure followed by recompression (interval of 10 minutes) to a pressure of 30 pounds (oxygen) for 25 minutes. Pressure was then lowered to atmospheric in 12 minutes, and oxygen inhalation continued for 17 minutes.

Preceded by a period of oxygen breathing (30 minutes) compression of the dog was again carried out at a pressure of 65 pounds for a period of 45 minutes followed by a 10 second decompression. After an interval of 12 minutes the dog was recompressed to a pressure of 30 pounds for 20 minutes (oxygen inhalation).

globin 26 per cent) which would appear to be incompatible with life (column 3, table 3). The subnormal blood pressure of the recovery period is conceivably accounted for by previous injury to the right ventricle (dilation) as a result of excessive resistance in the pulmonary circuit and of impaired circulation through the coronary vessels during the asphyxial period. Another possible factor in preventing complete blood pressure recovery is a paralysis of splanchnic vascular tone from spinal cord injury. In the experiments of Heller, Mager, and von Schrötter, spinal cord injury following a deprivation of blood supply was a frequent consequence of multiple gas emboli. Under the pressure conditions existing in our experiments, paralysis usually of the hind legs occurred regularly in unanesthetized dogs. An example of a blood pressure fall, probably the result of spinal cord injury, is given by experiment 23, table 4. In this experi-

ment, a precipitous drop in blood pressure took place under 30 pounds pressure with the dog breathing oxygen.

The maintenance of life under the conditions of these experiments depends, essentially, upon the integrity of the right ventricle, and upon its ability to propel blood through an obstructed pulmonary bed. The absorption of bubbles by compression and by oxygen inhalation leaves the animal in good condition as observed in experiments on unanesthetized dogs, unless irreparable damage has been done to the heart by oxygen lack or increased pulmonary resistance, or to the spinal cord from ischemia.

Oxygen and carbon dioxide content of the blood.—Blood samples in these experiments were drawn from the femoral artery and from the right atrium or ventricle by means of a glass cannula inserted into the external jugular vein. Of particular

TABLE 5

*Analysis of oxygen content of blood from anesthetized dogs rapidly decompressed from high pressure atmospheres**

EX- POSURE	PERIOD	VOLUME PER CENT OXYGEN CONTENT		ARTERIAL VENOUS DIFFER- ENCE	OXYGEN CAPACITY	PER CENT O ₂ SATURATION		PRESSURE CO ₂ ARTERIAL BLOOD
		Arterial	Venous			Arterial	Venous	
9†	Control	15.9	10.1	5.8	17.7	90	57	45
	Following decompression	5.4	0.5	4.9	22.4	24	2	59
	Recompression	17.9	7.9	10.0	20.3	88	39	
	Following recompression	5.9	2.3	3.6	22.8	26	10	
10‡	Control	20.6	17.0	3.6	22.8	90	75	
	Following decompression	14.6	7.7	6.9	26.1	56	30	
	Recompression	31.7§	20.0	11.7	27.3	100	64	
	Following recompression	26.0	7.3	19.6	29.8	90	24	

* Data from Behnke et al., *Am. J. Phys.*, 114: 526, 1936.

† Air inhaled during two-hour recompression period.

‡ Oxygen inhaled during two-hour recompression period.

§ 4.4 volumes per cent oxygen in physical solution.

interest was the occurrence of *hemoconcentration* shown by increased oxygen capacity of blood (table 5). In some tests it amounted to as much as a 30 per cent increase in cell volume. The hemoconcentration was thought to be due to a loss of fluid through capillaries damaged by asphyxia and possibly an increased mobilization of red blood cells from the spleen. The blood, moreover, was difficult to withdraw because of the tendency to clot. In histologic sections of the lungs, cell packing in blood vessels was a consistent finding.

The increased arterial-venous oxygen difference (exposure 10) is an indication of the slow circulation rate. The low values for arterial oxyhemoglobin reflect the derangement of pulmonary ventilation and circulation by the gaseous emboli. The phenomenon of especial interest is the continuance of cardiac contractions despite the presence of the greatly reduced hemoglobin in the arterial blood.

Variables affecting bubble formation.—In man, the factors responsible for bubble formation fall into two groups. In the first are those conditions which increase gas content of tissues, namely, the amount of fat, the degree and duration of exposure to pressure, and, in rapid ascent to high altitudes, exercise, which among other effects serves to introduce carbon dioxide into the circulation. In the second group are variables affecting the circulation of blood and the transport of gas from the tissues. Thus age, time of day, temperature, fright, injury of tissue, and the post alcoholic state all affect what may be termed "effective blood flow" through tissue.

In the numerous exposures in the low pressure chamber to simulated altitudes above 30,000 feet, the circulatory factors have been carefully evaluated. That age is a factor in the sense that the individual of 18 years is less susceptible to bends than is an individual 25 years old emphasizes the importance of adequate circulation as measured by the metabolic rate. The findings that bends are more apt to occur in the morning than in the afternoon, that fright produces peripheral vasoconstriction to interfere with gas transport, and that bends frequently occur at the site of old injury, all tend to emphasize the importance of the factor of effective blood flow and serve to explain not only the variation between individuals but in the same individual when he is subjected to the stress of decompression.

In effect, rapid decompression in the pressure chamber serves as a physiologic test for age. The more rapid the blood flow, the greater the capillary circulation, the less likely will bends occur.

Some conception of the meaning of effective blood flow through tissues is derived from comparing the tolerance of various animal species to rapid decompression following saturation exposures in high atmospheric pressures. Man tolerates a sudden drop in pressure of 2 atmospheres to 1; for the dog and cat, the ratio is 4 to 1; for the guinea pig, 5 to 1; and for the mouse, about 6 to 1. The pattern of tolerance follows roughly the relationship of basal metabolism to unit of body weight.

There is, perhaps, no other condition of comparable severity in which the circulation of blood throughout the body can be brought nearly to cessation and from which recovery occurs when the stress is removed.

Compressed air illness may be looked upon simply as a Naval and industrial problem arising from the presence of gas bubbles in the blood stream. When the body is recompressed, the symptoms disappear as the bubbles are reabsorbed.

On the other hand, if the bubbles are allowed to remain and accumulate, the injury becomes a disease and its protean manifestations of rash, pain asphyxia, and paralysis simulate those of an overwhelming infection. That this injury and disease can be studied by quantitative methods to reveal basic mechanisms of impaired and interrupted circulation makes possible additions to the science of medicine.

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CIRCULATION AND RESPIRATION IN FEVER¹

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CONTENTS

I. Introduction.....	403
II. Cutaneous Circulation.....	405
III. Oxygen Consumption. Metabolic Rate.....	409
IV. Respiratory Dynamics. Lung Volume and Its Subdivisions.....	410
V. Respiratory Quotient. Alveolar Air Carbon Dioxide. Blood Bicarbonate...	412
VI. Cutaneous Respiration. Loss of Carbon Dioxide through the Skin.....	413
VII. Blood Carbon Dioxide Combining Power.....	413
VIII. pH of the Blood and Various Secretions.....	414
IX. Tissue Gas Tensions.....	414
X. Pulse Rate.....	415
XI. Cardiac Output. Stroke Volume.....	416
XII. Circulation Time.....	417
XIII. Electrocardiogram.....	418
XIV. Arterial Blood Pressure. Peripheral Resistance.....	418
XV. Venous Pressure.....	419
XVI. Blood Volume.....	419
XVII. Capillary Filtration. Lymphatic Flow.....	421
XVIII. Renal Function.....	422
XIX. Gastrointestinal Function.....	423
XX. Hepatic Function.....	423
XXI. Cerebral Function.....	423
XXII. Comment.....	424

I. INTRODUCTION

The medical and lay writings of every era contain references to the changes in circulation and respiration occurring during fever. The importance with which physicians regard the study of the cardiovascular and pulmonary manifestations of fever in the handling of patients with febrile diseases is exemplified by the modern hospital chart, but few clinicians are familiar with the physiological mechanisms which underlie these phenomena. The growing interest in infectious diseases and in fever therapy makes a discussion of these mechanisms valuable at the present time, especially since many pertinent data have accumulated since Bazett's review (20) was written twenty years ago.

Fever may be classified under the following headings:

- A. Endogenous Fever
 - 1. Exercise
 - 2. Hypothalamic lesions
 - 3. Infection or tissue breakdown
- B. Fever Physically Induced
 - 1. Externally applied heat
 - 2. Diathermy

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The fever of exercise and of hypothalamic lesions will not be considered here, the former because it is not pathological and in addition is discussed in the recent review by Du Bois (59), the latter because it is uncommon and studies on its mechanism are incomplete.

Studies of the fever which follows injection intravenously of killed typhoid bacilli or live malarial parasites carried on in these laboratories (4) and elsewhere made it clear that an endogenous febrile reaction consists in phases which are fairly sharply defined and which follow in regular sequence. The appearance of the patient is distinctive and changes in cardiorespiratory function are different in each of these phases. For purposes of discussion the phases have been designated (1) prodrome, (2) chill, (3) flush and (4) defervescence. During the *prodrome*, which lasts for 30 to 90 minutes after the injection intravenously of killed typhoid organisms, the patient experiences only such non-specific complaints as fleeting aches and pains, mild headache, nausea and malaise. In the *chill* phase the patient becomes increasingly pale and cyanotic, but the skin is dry except perhaps for a few beads of perspiration on the forehead or upper lip; the rectal temperature rises, while the skin feels relatively cool, and rigors may occur. This period is called the "chill phase" irrespective of whether or not shaking chills actually occur, for if rigors do not occur spontaneously, they can be produced regularly by exposing the patient to a blast of cold air or by placing an ice cube in his hand (4, 76). Rigors can be terminated by covering or otherwise warming the patient, thereby diminishing but not necessarily abolishing completely the physiological changes characteristic of this stage. The chill phase lasts approximately an hour and one-half and passes over rapidly into the *flush* phase, which is characterized by the development of a diffuse, intense, bright red erythema together with drenching sweats. During this phase, which lasts about an hour, the rectal temperature maintains a high level, as does the skin temperature also. Gradually falling temperature and lessening flush and sweating initiate the phase of *defervescence* which continues for some hours.

There is a large literature detailing the results of fever induced by such physical means as the various forms of diathermy, infra-red radiation, hot air and hot baths. The fever produced by these means is not ushered in by a chill phase (126), but the flush phase which occurs resembles in many ways that of endogenous fever (126). There are, however, a number of important differences between the flush phase of endogenous fever and that which occurs during the course of fever physically induced. In the case of fever induced by hot baths, respiratory and cardiovascular dynamics are modified by the changes caused by immersion of the body in water. During the induction of fever by other physical procedures, the patient usually is wrapped in blankets or placed in a cabinet of some sort with his head protruding, so that he is surrounded by air which is hot and he therefore experiences not only the cardiorespiratory changes of fever, but also those which occur in a warm environment; vasodilatation is accordingly extreme (126). These phenomena have been fully discussed in the review articles by Bazett (20, 21, 22) and also annually in the Annual Review

of Physiology and will be commented on only where pertinent in the present work. Patients in such a hot environment or in a hot bath are no longer able to lose heat by convection and radiation from the skin. Accordingly fever induced by these means is usually characterized by inability of the body to use the skin for the dissipation of heat in a normal manner, so that an additional burden is placed on two other mechanisms for heat loss, i.e., (1) the formation of sweat (100) and (2) respiratory activity. Dehydration therefore develops rapidly with a decrease in blood volume (*v. infra*, Sect. XVI), and there is also an accentuation of the effects of hyperventilation beyond those seen in endogenous fever (*v. infra*, Sect. IV). When considerable dehydration develops, a decrease in perspiration finally occurs, placing an additional burden on the respiratory mechanism. In addition, the atmosphere surrounding the patient in whom fever is induced by physical means is often saturated with water vapor, so that the cooling effect of the evaporation of perspiration is lost as a mechanism for dispersing heat; this is also true of patients immersed in baths. In both cases therefore a still greater increase in hyperventilation occurs.

There are available a large number of studies of heat exchange in fever; there is no need to consider them in any great detail in this work, and they will be touched on only briefly where pertinent. The reader is referred to the review by Du Bois (59) for a full consideration of that subject.

II. CUTANEOUS CIRCULATION

The changes in cutaneous circulation which occur in fever are striking and are so important in initiating or influencing the other cardiovascular and the respiratory phenomena as to require that they be discussed first.

Although the circulation through the skin during the *prodrome* shows no detectable deviation from the normal, marked changes are present in all the other phases of the febrile reaction. Observation of the capillaries of the finger nailfold has shown that the *chill* phase is ushered in by an intense vasoconstriction which manifests itself by the disappearance of many capillaries and the narrowing of the rest, the blood flow through the remaining open capillaries being greatly slowed (4, 76). These changes are similar to those reported to occur in cutaneous capillaries after exposure to externally applied cold; the latter causes narrowing of the capillaries (89) and slowing of flow in them (61, 73, 89). Plethysmographic studies by Maragliano (163) revealed decreases in limb volume in the chill phase of febrile illnesses. Fremont-Smith *et al.* (76) ascribed all of these changes to spasm of the small arterioles. The only available studies of capillary pressure in the *chill* phase are those of Meldolesi (176) who found no change in patients with malaria, but these observations must be discounted because of inaccuracies in the method used. The observations of several authors who studied skin which was cooled directly or reflexly may, however, be considered analogous. Landis (147, 148) and Eichna and Bordley (61) used a direct method and Danzer and Hooker (52) employed a less accurate indirect method for measuring capillary pressure; all noted that exposure to cold was associated with a 30 to 70 per cent fall in pressure in the capillary loops in the nailfold. The mechanism of the cutaneous vaso-

constriction of the *chill* phase of an endogenous febrile reaction was shown to be activity of the sympathetic nervous system by Johnson, Osborne and Scupham (126), who demonstrated that spasm of the blood vessels of the skin during a chill following the injection of typhoid vaccine was absent in a sympathectomized limb and occurred only in an extremity innervated normally. Studies of cutaneous temperature by Perera (197) corroborate this observation. Sympathetic activity may at the same time give rise to the appearance of goose-flesh and a certain amount of sweating. The superficial veins appear narrowed, and blood is withdrawn from them with increasing difficulty (4). Blood from the antecubital or femoral veins contains very much less oxygen and more carbon dioxide than blood drawn before the onset of the chill phase (4). It is of interest in these connections that cooling the skin externally has also been shown to cause constriction of the cutaneous veins (56, 210, 213) and a decrease in oxygen content of venous blood (173, 175). In the *chill* phase of the febrile reaction the temperature of the blood from the superficial veins may fall, or at least fail to rise (248) parallel with the change in body temperature. Plethysmographic studies show a reduction in blood flow in the extremities (111, 126) in this phase; this represents mainly the blood circulating through the skin, since the flow through resting muscle is small (92, 142). No observations on the arteriovenous anastomoses have been reported, but in view of the fact that these vessels usually act in a manner similar to that of the arteries and veins (43, 44, 88), it is probable that they too are constricted. Cold external environmental temperatures have been shown to narrow the arteriovenous anastomoses (43, 44, 88), except when the temperature falls to extremely low levels when the anastomoses reopen (88, 89, 90).

The reduction in cutaneous blood flow may be sufficiently marked to result in a fall in skin temperature, according to Barr, Cecil and DuBois (16); Friedlander, Bierman and Silbert (77); Petersen and Müller (183, 198) and Perera (197); Perera (197) found no decrease in skin temperature over a sympathectomized extremity during the *chill* phase of a febrile reaction. When the temperature reaches a sufficiently low level, a reflex is activated and shivering commences. It should be noted, however, that experiments in animals have shown that perfusing the head with chilled blood also may cause generalized shivering. In the absence of actual shivering during the *chill* phase of a febrile reaction, there may be a variable amount of tensing of the muscles as the patient feels increasingly cold. If shivering does not occur, it can be brought on by cooling the skin locally by means of a blast of cold air or by the application of ice; these measures induce further vasoconstriction reflexly, thus lowering the skin temperature below the critical point at which shivering develops. The skin temperature at which the onset of shivering occurs during the *chill* phase of a febrile reaction has not been investigated, the reported studies having been made during exposure to low environmental temperatures (101, 229). Müller and Petersen (183) reported a fall in muscle temperature during the *chill* phase of fever, a finding not corroborated by Nedzel (189). The observations of Friedlander, Bierman and Silbert (77) on muscle temperatures are difficult to interpret.

A consequence of the marked change in cutaneous circulation is the diminution of heat loss through the skin noted during the chill phase of a febrile reaction (5, 16). Normally most of the heat formed in the body is dissipated via the skin, and the loss of this function accentuates the rise in temperature already initiated by the increased heat production (59) of the febrile reaction. It is of interest that the patient feels coldest while his body is storing the most heat.

Data bearing on the effect of external environmental temperatures on blood flow in the skin have been presented by many authors (1, 12, 74, 75, 91, 92, 94, 103, 111, 112, 142, 172, 210, 223, 226, 227, 231, 240, 241, 242, 246, 247), and a relation between the two has been established: flow varies roughly with temperature, when the temperature of the arterial blood remains essentially at normal levels. In the *chill* phase of a febrile reaction, however, the diminution in cutaneous blood flow is endogenous and is maintained in spite of the rise in the temperature of the blood entering the skin and accordingly it appears that a very severe degree of vasoconstriction due to marked sympathetic hyperactivity must be present.

At the onset of the *flush* phase cutaneous vasodilatation rapidly develops. Under ordinary circumstances a steadily rising body temperature might be expected to be associated with corresponding gradual increases in cutaneous flow, but in the endogenous febrile reaction the increase in flow in the skin is delayed and when it finally occurs, is sudden. The reason for this peculiarity is not clear, but an interesting parallel may be drawn between this phenomenon and one observed by Hewlett (111). That author noted that if the body is chilled externally for a time, warming does not cause the usual gradual increase in the circulation of an extremity and the blood flow remains unchanged until the environmental temperature has shown a considerable elevation, at which time the flow rapidly increases; a similar observation was recorded by Wilkins and Eichna (241). It is not unlikely that the onset of the *flush* phase of the febrile reaction involves a similar mechanism, the increasing warmth of the blood finally giving rise to a relaxation of the persistent vasoconstriction. The vasodilatation which occurs when the blood is warmed is neurogenic and is consequent not only to relaxation of vasoconstriction, but also to activity of sympathetic vasodilator fibres (67, 78, 91, 156, 157); a sympathectomized extremity will not show this reaction to warming (156). It is of interest that goose-flesh may again appear at this point, as in the case of the onset of sympathetic activity responsible for chilling. It is not clear whether the temperature of the arterial blood in the skin activates a reflex which causes vasodilatation or whether the temperature of the blood in the brain is the factor responsible for the generalized vasodilatation. The latter mechanism appears to have been established by Gibbon and Landis (78) in the case of the skin warmed externally. Moorhouse (182) noted an increase in the volume of the paw in animals in which the carotid blood was warmed.

Observation of the capillaries of the nailfold during an episode of endogenous chill and fever shows a rapidly developing vasodilatation at the beginning of the *flush*; the capillary dilatation persists throughout this phase (4, 76, 248). The

flow appears more rapid than normal, and all the visible vessels, capillaries and others, show active pulsation (4, 76). The blood flow through an extremity as measured by plethysmographic methods is increased in the *flush* phase of endogenous fever (111, 126); as pointed out above, the greater part of flow measured in this way represents flow through the skin, as the circulation of resting muscle is small. The limb volume, as measured with the plethysmograph, increases (163). The superficial veins become distended (4) and blood drawn from them is bright red. The temperature of this blood, relatively low during the *chill* phase (248), rises to a level comparable with the body temperature during the *flush* phase (248). Measurements of its oxygen content reveal levels within or close to the arterial range (4). A similar prominence of superficial veins (56, 156, 210, 213, 238), increase in capillary flow (73) and arterialization of venous blood (15, 75, 87, 120, 173) occurs when the body, or only the extremity studied, is warmed externally. Holling (120) found that arterialization of blood from the antecubital vein did not occur when heat was applied, if the return of blood from the hand was excluded, not an unexpected finding in view of the very large number of arteriovenous anastomoses in the hand as compared to the forearm. The capillary pressure probably rises during the *flush* phase of fever, for Landis (147), using direct, and other authors (52, 83, 155), using less accurate indirect methods of measurement, have demonstrated such a rise presumably consequent to arteriolar dilatation, when the skin flushes in response to direct heating or in response to heat applied over another part of the body. In the case of some patients who are experiencing a febrile reaction, however, the vasodilatation may be so marked as to result in a considerable fall in arteriolar pressure, so that capillary pressure may possibly show only slight increases.

The findings reported in fever induced by physical means are qualitatively similar to those observed in the *flush* phase of endogenous fever. Thus prominence of superficial veins in man has been noted in a hot bath which raised the rectal temperature (23). Fever induced by diathermy causes changes in capillary flow similar to those described in the *flush* phase of an endogenous febrile reaction (233, 248). Arterialization of venous blood has been described in animals with fever consequent to hot water (234) or air (70) baths and in dogs subjected to diathermy (186). Similar findings have been reported in human subjects in whom fever developed in hot air (3, 37, 50A, 51, 116, 195, 196) or hot water (150, 172) baths and after diathermy (28, 186). In addition, studies by means of plethysmographic or other methods have shown an increase in blood flow through the extremities in human subjects following the induction of fever by hot baths (91, 112, 126, 240, 241), by heated air (36, 112, 116, 126) and by diathermy (126). The increase in flow is detectable in the forearm and hand in patients with fever, according to Grant and Holling (91), whereas in patients in whom heat is applied externally so as to produce reflex vasodilatation without fever the increase in flow is limited to the hand.

Johnson, Osborne and Scupham (126) have shown that the flow through the skin is increased more by fever physically induced than by that which follows intravenous injection of typhoid vaccine. The increased cutaneous flow of fever is similar to that which occurs in a part locally heated, but is greater (240):

the increased cardiac output of fever (*v. infra*, Sect. XI) is probably the explanation for this observation. The cutaneous arteriovenous anastomoses open widely with local heating of a part (43, 44, 88) or during warming of the entire body (88); this occurs at approximately 40°C., while the arterioles dilate at approximately 35°C. (88). A single study has been made recording the opening of arteriovenous anastomoses in the skin in the *flush* phase of fever following the injection of typhoid vaccine (248). Shunting of the blood through these anastomoses causes the venous blood to become arterialized and is therefore responsible in part for the increased flow observed.

Vasodilatation and increased flow in the skin causes an increase in the rate of heat loss (16, 59), so that the body temperature tends to remain approximately at a level in spite of the continued abnormally great heat production. During the *flush* phase heat production and loss balance each other (16, 59). This is not entirely a direct consequence of increased flow and vasodilatation, however, since drenching perspiration accompanies the flush phase and accounts for much of the increased loss of heat. Several authors (97, 115, 122, 170, 242) have shown that sweating occurs over the extremities when the skin temperature reaches approximately 34°C. It is possible therefore that the rapid flooding of the chilled skin with blood at 40°C. which occurs at the onset of the *flush* phase during an episode of chill and fever quickly raises the skin temperature to or above the critical point, and a reflex is initiated which results in a sudden drenching sweat. It is to be noted, in addition, that the circulation of warmed blood through the brain may also give rise to sweating (97, 156), but considerable increases in the temperature of the brain must occur before sweating develops under these circumstances (200). In patients who have exhibited a severe chill reaction the sweating which develops with the flush phase may be delayed in its onset for 10 or 15 minutes. This is of interest since Kuno (143) has shown that previous chilling of the skin retards the appearance of sweating in response to increases in environmental temperature. In the case of fever induced by physical means sweating is likely to be more gradual in onset and is usually more profuse, since convection and radiation from the skin are no longer effective in the dissipation of heat. It has been demonstrated that the loss of the latter processes results in increased perspiration (100, 229). The marked dehydration which often occurs in fever physically induced may result, after a time, in some decrease in perspiration.

During *defervescence* the cutaneous circulation is not at first strikingly changed from that of the flush phase. Heat production falls (16, 59), however, and since heat loss is maintained at its previously high level, body temperature decreases. After a variable period of time the cutaneous circulation begins to return to normal, but a complete restoration to normal does not occur for many hours.

● III. OXYGEN CONSUMPTION. METABOLIC RATE

Many studies have demonstrated a parallelism between the degree of fever and the oxygen consumption or metabolic rate in febrile diseases (17, 29, 48, 49, 50, 159, 164, 194A), as well as in man after typhoid vaccine (4, 16, 59, 138);

Grollman (95) noted an increase in oxygen consumption after the injection intravenously of typhoid vaccine even in the absence of fever. The parallelism between metabolism and body temperature is, however, imperfect when rigors occur; under these circumstances the muscular activity associated with a shaking chill causes a much greater increase in metabolism than even the most marked degree of fever (16, 17, 101, 229). In the absence of rigors the muscular tensing which some patients exhibit as a reaction to sensations of cold in the *chill* phase may also elevate the metabolic rate somewhat.

Fever induced by hot air (109, 116, 138, 228) or water (24, 109) baths in man raises the metabolic rate to approximately the same degree as does endogenous fever; animals made febrile by hot baths (234) or diathermy (185, 187) also show an increased oxygen consumption. Diathermy was described by Kopp (138) as having a less marked effect than typhoid vaccine or a heating cabinet, a finding not confirmed by the data of Neymann and Osborne (191) or Simpson (219).

IV. RESPIRATORY DYNAMICS. LUNG VOLUME AND ITS SUBDIVISIONS

There are no constant changes in respiration during the *prodromal* phase of the endogenous febrile reaction. The *chill* phase, on the other hand, is characterized by a considerable increase in respiratory rate and minute volume (4), the tidal air volume decreasing somewhat (4). The shallow breathing may be reflected in a small decrease in arterial blood oxygen saturation (4), although the latter may be unchanged.² The increase in respiratory minute volume is appreciably greater than the rise in oxygen consumption. If rigors occur, a very large increase in respiratory rate and minute volume is observed. During the *flush* phase of an endogenous febrile reaction in man the respiratory rate usually falls and minute volume usually decreases somewhat relative to oxygen consumption, while the tidal air volume is restored approximately to the normal value (4). The respiratory minute volume, however, is often still somewhat increased out of proportion to the oxygen consumption (4). Knipping, Lewis and Moncrieff (133) have also noted this phenomenon in patients with a variety of febrile diseases.

A large number of reports containing data on respiratory dynamics in fever induced by physical means have been published. An increase in respiratory rate is usually described in human subjects in whom fever is induced by heating cabinets (19, 235, 236), hot baths (19, 23, 91, 150) or diathermy (28, 69, 160, 186). In man hot air (19, 219, 236) or water (19, 62, 98, 117, 150) baths and diathermy (28) which raise body temperature also increase respiratory minute volume; hot water baths are reported to increase it more than hot air (19). Adolph (3) found no striking increase in respiration in man made febrile by exposure to hot air. Variable changes in tidal air volume occur in human subjects

² The present discussion disregards the shift to the right in the oxygen dissociation curve observed by Hüfner (123, 124, 125), Barcroft (13, 14) and Brown and Hill (32) on heating blood *in vitro*, since the changes occurring in the range of temperature considered here are small.

who develop fever in hot air (19, 236) or hot water (19, 150) baths. The hyperventilation which occurs in fever physically induced may result in a lowering of arterial blood oxygen saturation (105, 160).

In animals, heating cabinets (41, 70, 234), hot baths (234) and diathermy (107, 185, 187, 239) cause fever and also give rise to hyperventilation. The respiratory rate in animals made febrile by hot air or water baths (41, 234), or diathermy (107, 135, 185, 186, 187, 239) is greatly increased. Shallow respiration in animals made febrile by physical means is described by various authors (107, 185, 234). Uyeno (234) correlated this type of breathing with a decrease in arterial oxygen saturation. Several reports mentioning increased tidal volume, however, have also been published (41, 239).

The hyperventilation of fever is associated with a fall in carbon dioxide concentration of the expired air (4, 114, 185).

The increased respiratory activity which occurs during fever is useful in that the elimination of heat via the lungs is increased. It is of interest that during the course of a bout of endogenous fever hyperventilation is usually most marked during the *chill* (4) phase, when elimination of heat through the skin falls to a marked degree. In fever caused by hot air and hot water baths the heat loss through the skin is also reduced and extreme degrees of hyperventilation consequently may occur.

The mechanism which causes the increased respiratory activity of fever has been studied by a number of authors. Kahn (128) and Heymans (114) warmed the blood perfusing animals and observed a rise in rectal temperature and an increase in respiratory activity. In Kahn's experiments (128) the warmed blood was infused into the carotid artery and a considerable increase in respiratory rate occurred before a detectable rise in rectal temperature was noted. Moorhouse (182) performed similar experiments and observed tachypnea and a decrease in the volume of the tidal air. The concept that the increased respiratory activity seen in fever was partly a consequence of the flow of abnormally warm blood into the respiratory centers was established by Heymans and Ladon (113) by means of cross-circulation experiments. These authors found that perfusion of the isolated head with heated blood caused an increase in respiratory rate until the temperature exceeded 45°C. It appears that the respiratory centers react to small changes in the temperature of the blood. An additional mechanism may, however, operate during the *chill* phase or at least part of it. Slowed blood flow through the brain (*v. infra*, Sect. XXI) results in a tendency toward the accumulation of carbon dioxide in the tissues which may be exaggerated by increases in metabolic rate. This accumulation of carbon dioxide in the respiratory center acts as a stimulant to respiration until the resultant hyperventilation gives rise to a sufficient degree of lowering of arterial blood carbon dioxide to compensate for the effects of stasis. It is to be noted, however, that the hyperventilation of fever persists in spite of marked lowering of blood carbon dioxide levels and similar though less marked changes in hydrogen ion concentration.

Data on changes in the lung volume or its subdivisions during fever are scanty.

Hick *et al.* (115) found an increase in vital capacity in subjects who developed fever in a hot air chamber and concluded that blood was drawn from the lungs into the skin as a consequence of cutaneous vasodilatation. Hasselbalch (106) and Budelmann (35), on the other hand, described a decrease in vital capacity in subjects in a hot bath compared to the values found in cold or neutral baths, but even neutral baths lower it somewhat (99). Knipping, Lewis and Moncrieff (133) found the vital capacity lowered in febrile diseases. In a study (4) of the lung volume and its subdivisions during an episode of chill and fever following the intravenous injection of typhoid vaccine, no changes were found during mild *chill* reactions, but in severe *chill* reactions a fall in reserve and complemental airs and vital capacity and a small rise in residual air were noted. There was an increase in the ratio residual air/total capacity, indicating the development of some degree of pulmonary congestion. The changes were small, however, and intrapulmonary factors can largely be ruled out as the cause of the severe hyperventilation observed during this phase. During the *flush* phase the abnormal findings were largely or completely restored to normal. •

V. RESPIRATORY QUOTIENT. ALVEOLAR AIR CARBON DIOXIDE. BLOOD BICARBONATE

The above described increase in respiratory minute volume in excess of the simultaneous increases in metabolism during fever leads to a washing out of carbon dioxide from the alveolar air and consequently from the blood also. This may be detected as a rise in respiratory quotient which has been noted in the absence of muscular activity in human subjects in the fever which follows the injection intravenously of typhoid vaccine (4) and that which occurs in hot baths (23, 62, 109) or during exposure to heated air (109, 228). It should be borne in mind, however, that the increased respiratory quotient of fever may be related in part to a disproportionate increase in carbohydrate utilization as the metabolic rate rises. The rise in respiratory quotient observed by earlier workers (16) during rigors consequent to the injection intravenously of typhoid vaccine is difficult to interpret because of the occurrence of marked and repeated muscular contractions.

The alveolar air carbon dioxide concentration falls rapidly during the *chill* phase of an endogenous febrile reaction (4) and is maintained at a low level thereafter. Low alveolar air carbon dioxide concentrations have also been described in various febrile illnesses (71, 199). Fever which occurs in human subjects exposed to heated air (3, 19, 196) or in hot baths (19, 23, 98, 117, 150) also results in a decrease in the carbon dioxide concentration of alveolar air. A similar finding has been noted in animals exposed to heated air (41).

Studies of the blood bicarbonate in man have demonstrated a decrease in blood level in malaria (34), influenza and other febrile illnesses (129, 137) and after the intravenous injection of typhoid vaccine (4). Similarly fever induced in human subjects by heated air (3, 37, 50A, 51, 130, 196, 219, 235, 236), by hot baths (137, 150) and by diathermy (27, 28, 160, 186) also is associated with a fall in the level of the blood bicarbonate.

Animals made febrile by the injection of Shiga toxin (169) or *B. Coli* vaccines

(10, 169), or by such physical means as heating cabinets (41, 70, 169), hot baths (7) or diathermy (108, 135, 186, 187) show similar changes in the blood.

Increase in the tension of aqueous vapor at high temperatures (98) lowers the alveolar air carbon dioxide slightly, but this plays a very minor part in causing the changes observed. Adolph (3), who described only an inconstant occurrence of hyperventilation in fever caused by exposure to hot air, felt that loss of carbon dioxide through the skin was the important factor in causing the lowering of blood bicarbonate; as will be discussed below (Sect. VI), it is unlikely that his conclusion is valid. The available evidence strongly favors the view that hyperventilation is the sole important cause of the changes in alveolar air carbon dioxide and the blood bicarbonate concentrations noted by all who have made the appropriate studies.

VI. CUTANEOUS RESPIRATION. LOSS OF CARBON DIOXIDE THROUGH THE SKIN

Studies of cutaneous respiration have not been made during fever, but pertinent data based on observations on the effects of warm environmental temperatures reported by several workers are available. Oxygen is absorbed and carbon dioxide is eliminated through the skin in amounts which vary with the temperature (18, 63, 170, 214, 216). This relationship may be a consequence of the accelerated cutaneous blood flow which accompanies rising temperatures rather than vasodilatation, for vasodilatation which follows the injection of pilocarpine does not increase cutaneous respiration (64). At ordinary environmental temperatures the cutaneous respiration amounts to 1 or 2 per cent of the total respiratory exchange of human subjects at rest (63, 216); it is agreed that the cutaneous respiratory quotient averages approximately 1.4 (63, 216). The curve of increase of cutaneous respiration with rising skin temperature shows a sharp rise at approximately 34°C., the rate of increase in carbon dioxide excretion rising more rapidly than that of absorption of oxygen. This fact is of interest, since several authors (97, 115, 122, 170, 242) have shown that 34°C. is the temperature at which sweating begins over the extremities. At a skin temperature of 40°C. the excretion of carbon dioxide amounts to only approximately 5 cc. per minute for the entire body. The pH of sweat, normally acid, becomes alkaline in fever (*v. infra*, Sect. VIII), so that in addition to the increased amounts of free carbon dioxide lost through the skin at high temperatures, bicarbonate must appear in the perspiration. On the other hand, the excretion of carbon dioxide through the skin has been shown to vary with the carbon dioxide content of the blood (215) which falls in fever (*v. supra*, Sect. V). Accordingly it is concluded that the loss of carbon dioxide through the skin must play a very small part in the hypocarbia which is a constant finding in uncomplicated fever.

VII. BLOOD CARBON DIOXIDE COMBINING POWER

A fall in alkali reserve has been described in human subjects with malaria (34) and in dogs made febrile by the injection of *B. Coli* vaccines (10). On the other hand, fever caused by physical means gives rise to no change (98) or a minor

rise (27, 37) or fall (186, 237). In animals a fall in carbon dioxide combining power is the rule (7, 8, 70, 186). Some decrease in blood carbon dioxide combining power is to be expected after continuous, prolonged blowing off of large amounts of carbon dioxide by hyperventilation. Lowering of the alkali reserve when it occurs during short bouts of fever is not an indication of acidosis, but is largely a late consequence of hyperventilation. It is possible that the more marked increases in respiratory activity in animals with fever account for the above discrepancies.

Acidosis manifested by a lowered alkali reserve is a common finding in infections which have persisted for some days (154, 174), but this phenomenon need not be discussed here, as it is probably conditioned by deficient food, salt and fluid intake, the continued loss of base by sweating and in some instances by vomiting or diarrhea.

VIII. pH OF THE BLOOD AND VARIOUS SECRETIONS

The hyperventilation of fever and its resultant hypocarbia gives rise to an increase in the pH of the blood; this has been noted in man in malaria (34), in influenza and other febrile diseases (129, 137, 217) and after the intravenous injection of typhoid vaccine (4). Similar changes, usually greater in degree, have been described in human subjects made febrile by heating cabinets (2, 3, 37, 50A, 51, 219), hot baths (98, 137, 150) and by diathermy (27, 28, 191A). The data of Fishberg and Bierman (69), which show a fall in blood pH in patients exposed to short radio waves, are discordant.

Studies in animals also reveal considerable elevation in blood pH in fever caused by heating cabinets (41, 70) and diathermy (108, 135).

Changes in urinary pH during the *chill* phase of endogenous fever cannot be studied since little urine is formed (76). However, specimens of urine voided during the fever produced in man by hot air (3, 19, 37, 195), by hot baths (19, 23, 150) and by diathermy (27, 28) are usually described as more alkaline than those obtained before induction of the fever. The change in the reaction of the urine during fever must be a consequence of the excretion of fixed base to compensate for respiratory alkalosis. In harmony with this conclusion is the fact that all authors who have studied the urinary excretion of ammonia have reported a fall (19, 37, 150).

Studies of the pH of sweat have been made in fever in man caused by hot air (2, 3, 37, 167, 195) or hot baths (23) and here too an increase in alkalinity is a common finding; ammonia content is said to be increased (27). Fishberg and Bierman (69) reported a slight fall in pH of the sweat in fever induced by physical means, but since their control levels were incredibly low, i.e., about 4.1, it is concluded that there was some gross error in their technique.

A single group of observations (195) records the fact that the saliva commonly becomes more alkaline in patients who develop fever in a heating cabinet.

IX. TISSUE GAS TENSIONS

Rosenbaum (203) showed that hyperventilation causes the loss of large amounts of bicarbonate from the tissues. Studies of the tissue gas tensions have

been made on man or animals in hot baths by Sibree (218), Campbell (38) and Schott (208). All report lowering of carbon dioxide tension, not an unexpected finding in the light of the above discussed changes in respiration and in the blood. Campbell (38) found that the oxygen tension rose in the skin but not the abdominal cavity, which is in harmony with the concept that arterialization of the venous blood occurs in the skin in the flush phase. Schott (208), however, noted no such change in cutaneous oxygen tension. Shifts in the blood hemoglobin dissociation curve due to alkalosis appear to be unimportant.

• X. PULSE RATE

The rapid pulse rate of fever has been the object of study by clinicians for centuries, and a relation between the degree of tachycardia and that of fever is accepted in almost all diseases.

Following the injection of typhoid vaccine, the curve of pulse rate in man is roughly parallel with that of temperature (4, 95, 126, 211). Perera (197) found an initial fall in some cases. Similarly, the pulse also becomes rapid in man in fever induced by hot air (3, 19, 50A, 57, 81, 126, 167, 206, 207, 219, 228, 235) or hot water (19, 23, 80, 91, 110, 117, 126) baths or by diathermy (69, 126, 160). Animals made febrile by hot air (41) or diathermy (239) exhibit the same phenomenon. In normal man Lyon (162) found that an average rise of 9.1 beats per minute in pulse rate occurs for each degree F. rise in rectal temperature; in patients with complete heart block the average rise is 3.8 beats per minute per degree F. according to Gilchrist (80).

Heating the blood perfusing an animal increases the pulse rate (114, 128, 131, 151, 171). In Kahn's experiments (128) the infusion of warmed blood into a carotid artery accelerated the pulse before a detectable rise in body temperature occurred; this suggests that some cerebral center was being stimulated, thus giving rise to tachycardia through a nervous mechanism. The similar experiments of Moorhouse (182) support this concept. Kisch (131), however, showed that this acceleration consequent to warming of the blood occurred when the heart was denervated, and Knowlton and Starling (134) observed it in the heart-lung preparation. It is therefore to be concluded that a rise in temperature in the sino-auricular node results in an increase in pulse rate; the possibility that warming certain cardiomotor centers in the brain has a similar effect cannot, however, be ruled out.

Knowlton and Starling (134) emphasized the fact that the rising pulse rate which follows warming of the infused blood in a heart-lung preparation is not associated with an increase in cardiac output. Clinical observation on patients with shock due to infection where extremely rapid pulse rates are the rule also indicates the same lack of relation in fever.

The relative slowing of the pulse in typhoid fever and its exaggerated increase in low grades of hyperpyrexia associated with some instances of rheumatic fever, tuberculosis and other diseases have been utilized in diagnosis. Differences in the degree of increase in pulse rate with fever in different diseases have not been explained; this problem is not related to the present discussion and will not be considered here.

XI. CARDIAC OUTPUT. STROKE VOLUME

A few studies of the minute volume output of the heart in patients with fever have been made, with increases described by Bjerl w and Liljestrand (29) in recurrent fever, by Dautrebande (53) in a fever of unknown etiology, by Mobitz (178, 179) in malaria, by Pellegrini in various diseases (194A) and by Grollman (95) during the reaction to typhoid vaccine. The last named reported that the increase in cardiac output was not in relation to the degree of fever, while the others found that such a relation existed. Starr and Jonas (224) surprisingly found no rise in cardiac output in patients with febrile diseases studied by means of the ballistocardiograph. In the studies of Bjerl w and Liljestrand (29) the cardiac output varied with oxygen consumption so that the arteriovenous oxygen difference was unchanged. In Pellegrini's studies (194A) the arteriovenous oxygen difference was variable. Dautrebande (53), however, found an increase in cardiac output in excess of the rise in metabolism, and the arteriovenous difference was lowered. In studies made here (4) the cardiac output was found to vary in the different phases of the febrile reaction following intravenous injection of typhoid vaccine. The *prodrome* caused no change in the output of the heart, but the *chill* phase was associated with a decrease in the minute volume flow, or in the patients with mild chill reactions a failure of the cardiac output to increase with the oxygen consumption; the arteriovenous oxygen difference increased in all cases. The rise in arteriovenous oxygen difference varied with the intensity of the chill. In severe *chill* reactions marked decreases in cardiac output and rises in arteriovenous oxygen difference were associated with the development of a shock-like syndrome and hypotension. During the *flush* phase, on the other hand, an increase in the output of the heart considerably in excess of the rise in oxygen consumption was found, with a consequent decrease in arteriovenous difference. Some restoration toward the normal relation between cardiac output and oxygen consumption occurred in *defervescence*, the absolute value for cardiac output still being increased. Although these changes were parallel to those which occurred in the skin, it is doubtful that the latter caused the former. The flow through the skin in man at ordinary temperatures is probably not much more than 150 cc. per minute for the entire body, a very small part of the total left ventricular output of approximately 5 liters, and the reduction of flow which occurs in the *chill* phase would not therefore make any noticeable difference in the venous return and thereby in the output of the heart. Similarly, the fact that in the *flush* phase the skin flow increases many times would also have little influence on the cardiac output. The flow through resting muscle is also small (92, 142). Changes in visceral flow are much more important in relation to the cardiac output; the renal blood flow, which shows definite changes in the various phases of fever (*v. infra*, Sect. XVIII) amounts to a fifth or a quarter of the total left ventricular output and flow through other abdominal viscera and the brain must make up most of the rest.

Studies in human subjects who develop fever in heated air must be interpreted with caution, since a warm environment, even in the absence of the development of fever, causes a small increase in cardiac output as indicated by a slight fall

in arteriovenous oxygen difference (96, 209, 210). Observations made in man during immersion in hot baths must be interpreted in the light of the fact that even neutral baths increase cardiac output (31, 24). Human subjects who develop fever in hot baths or on exposure to heated air show an increased cardiac output (24, 31, 35, 53, 62, 109, 110, 116, 153), the arteriovenous oxygen difference being described as decreased in heated air (109, 116), or increased (24) or decreased (53, 62, 109) in hot baths.

Studies of the cardiac output in animals with fever are few. Heymans (114) observed an increase in the volume of the blood flow when the blood perfusing an animal was heated. Uyeno (234), in a careful study by means of the direct Fick method, found an increase in cardiac output in animals made febrile by being heated by lamps or in hot baths; the data presented in his paper do not permit an evaluation of his conclusion that the arteriovenous oxygen difference is increased.

It is clear that except in the *chill* phase of endogenous fever a considerable increase in cardiac output and consequently cardiac work occurs when the body temperature is elevated. This is a useful reaction, since it brings warmed blood to the skin and lungs for cooling and tends to prevent excessively great rises in body temperature.

It was pointed out by Knowlton and Starling (134) that the acceleration of heart rate which occurs when the blood is heated does not necessarily signify an increase in cardiac output. Similarly it has been found in man (4, 29) that the pulse rate is a poor indicator of changes in cardiac output in fever, since it often increases more than the blood flow and may rise when the cardiac output falls. The stroke volume is accordingly often decreased, an observation also recorded in animals made febrile in a heating cabinet (41). •

XII. CIRCULATION TIME

Acceleration of the circulation time has been noted in various febrile illnesses, including tuberculosis and pneumonia (55, 82, 136, 152, 158, 212, 230, 245); Hitzig's finding (119) of normal ether and saccharine circulation times in pneumonia cannot be explained.

The circulation time in general is usually found to vary with the cardiac output. However, measurements of circulation time which utilize the injection of the test substance into an arm vein are influenced by an additional factor, namely, the temperature of the skin of the arm. Local cooling of an extremity slows the arm-to-carotid (cyanide) or arm-to-tongue (decholin or calcium) time, while local warming accelerates them (146, 221, 225). Accordingly changes in circulation time cannot be utilized to estimate the degree or even the direction of variations in cardiac output during an episode of chill and fever.

During the *chill* phase of the febrile reaction which follows the injection intravenously of typhoid vaccine in human subjects, the arm-to-tongue time is slowed (4). This may be related to a fall in cardiac output or may be the consequence of decreased temperature of the skin, or both. The *flush* phase of

the febrile reaction to typhoid vaccine is associated with acceleration of the circulation time (4). This is probably the combined effect of increased cardiac output and elevated cutaneous temperature. Kopp (139), Kvale and Allen (145) and Himwich *et al.* (118) usually found the circulation time accelerated in fever after the injection of typhoid vaccine, but the changes were often unexpectedly small for the degree of fever, and in some instances were absent. This finding is to be explained on the basis of the fact that apparently no attempt was made by these authors to differentiate fever occurring during the *chill* phase from that occurring in the *flush* phase. Fever induced in animals by the injection of blood was shown many years ago to be associated with accelerated blood flow, as measured by means of a stromuhr (26).

Fever physically induced in man by heating cabinets (57, 140; 235), electric blankets (139), and diathermy (132, 139) accelerates the circulation time greatly. Of particular interest in relation to the problem of shock in fever are the data of Kopp (139) which show that when the arterial blood pressure falls to low levels during fever therapy the circulation time, previously accelerated, becomes slowed.

XIII. ELECTROCARDIOGRAM

Although many studies of the electrocardiogram in various infectious diseases have been reported, only a few studies of the effects of artificially induced fever are available (41, 42, 72, 141, 219, 235). Aside from changes in rate, the most consistent alteration in the electrocardiogram is a decrease in amplitude or inversion of the T wave in one or more leads.

XIV. ARTERIAL BLOOD PRESSURE. PERIPHERAL RESISTANCE

A variety of changes in arterial blood pressure, usually minor in degree, have been reported to occur in man in endogenous fever and in fever physically induced (3, 19, 23, 24, 91, 110, 117, 140, 160, 167, 191A, 194A, 206, 207, 235). In many instances an increase in pulse pressure was noted (3, 126, 140, 167, 235). In studies made here (4) no change occurred in arterial blood pressure in the *prodromal* phase. Often no change likewise was noted in the *chill* phase, but many patients at times exhibited a slight degree of hypertension; Scully (211), Chasis *et al.* (40), Meldolesi (176) and Perera (197) also noted hypertension in the *chill* phase of the reaction to typhoid vaccine. On the other hand, a severe *chill* reaction has been found to be associated in many instances with profound hypotension. The onset of the *flush* phase is regularly associated with a slight or moderate fall in both systolic and diastolic levels (4, 176, 211).

Experiments in animals with endogenous fever (26, 177) or fever physically induced (41, 190, 239) likewise yielded a variety of changes. Heymans (114) found that perfusion of the head with heated blood causes no change in systemic arterial pressure, while Kahn (128) observed a rise.

Variations in the calibre of the blood vessels and in the volume of blood flow in the skin and viscera (*v.* Sect. II, XVIII, XIX, XX, XXI) must be associated with marked changes in peripheral resistance. Measurements of local changes in peripheral resistance cannot be made, but the *average* peripheral resistance

may be estimated from the cardiac output and mean blood pressure. No changes in average peripheral resistance occur in the *prodromal* phase. The *chill* phase may be characterized by only slight changes or by a considerable increase. Apparently the change in blood pressure in this phase is a reflection of vasoconstriction on the one hand and a variable decrease in cardiac output on the other. If the latter is great, hypotension develops in spite of marked vasoconstriction. During the *flush* phase, in spite of considerable increases in cardiac output, the widespread vasodilatation which occurs results in a fall in blood pressure levels. Fever physically induced also lowers peripheral resistance (41).

XV. VENOUS PRESSURE

Although the calibre of the superficial veins is greatly diminished in the *chill* phase and increased in the *flush* phase, only slight changes in the venous pressure occur in fever (4, 176). Hooker (121) and others (56, 213) many years ago showed that variations in the calibre of veins need not be associated with changes in pressure within them. Meldolesi (176) found venous pressure slightly elevated, but the present authors (4) found a small decrease in the *chill* phase in the absence of rigors. It is interesting in this regard that the cutaneous vasoconstriction which results from the local application of cold may also result in a slight fall in venous pressure (56). The occurrence of rigors with a febrile episode results in a rise of several centimeters in venous pressure (4), depending on the vigor of the muscular contractions. A significant fall in venous pressure was noted in some patients who showed a considerable decrease in arterial pressure (4). In all cases the venous pressure returned to or toward normal during the *flush* phase of the reaction to typhoid vaccine (4). Hot baths are said to elevate the venous pressure (35), more in cardiac patients than in normal subjects.

XVI. BLOOD VOLUME

Reports of studies in man of changes in blood concentration, based on measurement of hematocrit or plasma protein or both, usually are interpreted as indicating hemodilution in various febrile diseases (6, 181, 205), while hemoconcentration has also been described in some instances (6). In addition an increase in plasma volume has been described (222) in febrile diseases in man. In animals (180) peritonitis has been reported to be associated with hemoconcentration.

Measurements of plasma volume and hematocrit in human subjects (4, 79) following the intravenous injection of typhoid vaccine have shown no change in the former throughout the entire episode of chill and fever; the hematocrit (4, 79) or erythrocyte count (202) is also unchanged or may rise very slightly. Patients in the *chill* phase of malaria or sodoku, or the reaction to typhoid vaccine, who are given fluids by mouth, show hemodilution as well as dilution of the cerebrospinal fluid (76); this occurs apparently as a consequence of the cessation of urine formation in this phase. The changes in density described by

the febrile reaction to typhoid vaccine is associated with acceleration of the circulation time (4). This is probably the combined effect of increased cardiac output and elevated cutaneous temperature. Kopp (139), Kvale and Allen (145) and Himwich *et al.* (118) usually found the circulation time accelerated in fever after the injection of typhoid vaccine, but the changes were often unexpectedly small for the degree of fever, and in some instances were absent. This finding is to be explained on the basis of the fact that apparently no attempt was made by these authors to differentiate fever occurring during the *chill* phase from that occurring in the *flush* phase. Fever induced in animals by the injection of blood was shown many years ago to be associated with accelerated blood flow, as measured by means of a stromuhr (26).

Fever physically induced in man by heating cabinets (57, 140, 235), electric blankets (139), and diathermy (132, 139) accelerates the circulation time greatly. Of particular interest in relation to the problem of shock in fever are the data of Kopp (139) which show that when the arterial blood pressure falls to low levels during fever therapy the circulation time, previously accelerated, becomes slowed.

XIII. ELECTROCARDIOGRAM

Although many studies of the electrocardiogram in various infectious diseases have been reported, only a few studies of the effects of artificially induced fever are available (41, 42, 72, 141, 219, 235). Aside from changes in rate, the most consistent alteration in the electrocardiogram is a decrease in amplitude or inversion of the T wave in one or more leads.

§ XIV. ARTERIAL BLOOD PRESSURE. PERIPHERAL RESISTANCE

A variety of changes in arterial blood pressure, usually minor in degree, have been reported to occur in man in endogenous fever and in fever physically induced (3, 19, 23, 24, 91, 110, 117, 140, 160, 167, 191A, 194A, 206, 207, 235). In many instances an increase in pulse pressure was noted (3, 126, 140, 167, 235). In studies made here (4) no change occurred in arterial blood pressure in the *prodromal* phase. Often no change likewise was noted in the *chill* phase, but many patients at times exhibited a slight degree of hypertension; Scully (211), Chasis *et al.* (40), Meldolesi (176) and Perera (197) also noted hypertension in the *chill* phase of the reaction to typhoid vaccine. On the other hand, a severe *chill* reaction has been found to be associated in many instances with profound hypotension. The onset of the *flush* phase is regularly associated with a slight or moderate fall in both systolic and diastolic levels (4, 176, 211).

Experiments in animals with endogenous fever (26, 177) or fever physically induced (41, 190, 239) likewise yielded a variety of changes. Heymans (114) found that perfusion of the head with heated blood causes no change in systemic arterial pressure, while Kahn (128) observed a rise.

Variations in the calibre of the blood vessels and in the volume of blood flow in the skin and viscera (*v. Sect. II, XVIII, XIX, XX, XXI*) must be associated with marked changes in peripheral resistance. Measurements of local changes in peripheral resistance cannot be made, but the *average* peripheral resistance

may be estimated from the cardiac output and mean blood pressure. No changes in average peripheral resistance occur in the *prodromal* phase. The *chill* phase may be characterized by only slight changes or by a considerable increase. Apparently the change in blood pressure in this phase is a reflection of vasoconstriction on the one hand and a variable decrease in cardiac output on the other. If the latter is great, hypotension develops in spite of marked vasoconstriction. During the *flush* phase, in spite of considerable increases in cardiac output, the widespread vasodilatation which occurs results in a fall in blood pressure levels. Fever physically induced also lowers peripheral resistance (41).

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Rogers (202) in the blood of patients with malaria or a typhoid reaction are difficult to interpret.

Hemoconcentration was noted in animals made febrile by *B. Coli* (10, 11) but, on the other hand, actual measurements of blood volume by the carbon monoxide method in such dogs or in dogs which developed fever after the injection of a Shiga toxin have demonstrated only a slight and probably insignificant increase (169). The plasma volume in these animals was calculated from the total red cell volume and the hematocrit and appeared to be elevated during the fever (169).

The effects of fever physically induced on the blood volume in man have been investigated by a number of authors. Studies based on changes in plasma protein or hematocrit in human subjects exposed to air hot enough to elevate body temperature show the occurrence of hemodilution (19, 116, 235), no change (37) or hemoconcentration (51, 202, 236), while baths cause hemodilution (19) or concentration (23, 130). Diathermy fever causes no change (28) or hemoconcentration (27, 79, 160, 186). The discrepancies may be the consequence of varying degrees and durations of fever in the experiments cited. An important source of error in the studies based on hematocrit changes is the fact that venous blood is arterialized in fever (*v. supra*, Sect. II) which may result in a lowering of its hematocrit.

Studies of plasma volume in man exposed to heated air show small increases (116), no change (204) or, after a time, a fall (81). Hot baths are reported to cause a rise in plasma volume (244) with no change in hematocrit. The careful studies of Gibson and Kopp (79) demonstrate a definite difference between the fever of the reaction to typhoid vaccine and that induced by such physical means as lamps, heating cabinets and diathermy in that the former gives rise to no change in plasma volume, while the latter causes marked decreases. These differences between the two types of fever are related to the more profuse sweating which characterizes fever physically induced. The changes in plasma volume have been correlated with the occurrence of shock (79).

Observations on animals have been reported to reveal hemoconcentration (7, 8) in baths and in a heating cabinet (70, 161). On the other hand, the plasma volume of dogs made febrile by exposure to radiant heat has been described as increased (169). Hemoconcentration has been recorded in animals with diathermy fever (180, 186) and measurements of blood volume by the carbon monoxide method show a decrease (135, 168). Conclusions based on measurements of hematocrit in dogs are likely to be erroneous, for Palitz (194) has shown that while fever physically induced in that species results in an elevated hematocrit, this effect is abolished by splenectomy. The spleen of the dogs has been conclusively demonstrated to have contractile powers, but that of man has not, so that the application of Palitz's conclusions (194) to man is not warranted at this time.

The above-discussed observations appear at first to be completely divergent, making any valid general conclusion impossible, but actually this is not the case. One conclusion that may be drawn is that observations based solely on

studies of hematocrit in fever are likely to give rise to error because of the arterialization of venous blood in man and other species and because of the activity of the spleen in dogs. Calculations of plasma volume from the hematocrit and the total erythrocyte volume as measured by the carbon monoxide method may also be somewhat misleading. Another valid conclusion is that the fever which follows the injection of typhoid vaccine is not associated with changes in plasma or total blood volume unless fluids are given, in which case hemodilution may occur, at least during the *chill* phase. In the case of fever physically induced, the profuse sweating may, if protracted, give rise to hemoconcentration and a decrease in plasma volume severe enough to cause collapse. The marked changes in cutaneous and renal blood content in endogenous and other fevers are apparently counterbalanced by simultaneous changes in the opposite direction in other parts of the body.

XVII. CAPILLARY FILTRATION. LYMPHATIC FLOW

The changes in capillary circulation which occur during a febrile episode might be expected to be accompanied by changes in the rate of filtration through the capillary wall. Thus the marked vasodilatation and increase in capillary pressure which occur in the *flush* phase should exaggerate outflow. Measurements by Drury and Jones (58) and by Landis and Gibbon (149) show increased filtration with rising environmental temperatures, but only when the venous pressure is elevated above 20 cm. of water (149); it is possible that the method used does not detect increased filtration at lower filtering pressures. The effects of temperature on filtration are complex in that they include the consequences of vasodilatation, increased blood flow and possibly changes in capillary permeability. The rate of reabsorption of tissue fluid is not influenced by temperature (149) except when the latter is below 15°C.; this level is outside the range encountered in the body except for skin exposed to low environmental temperatures. Capillary permeability is apparently not influenced by fever (225A).

Only a few data on lymphatic flow are available. McCarrell (165) studied the effects of the direct heating of the nasopharyngeal mucosa on lymphatic flow in dogs and found an increase at temperatures above 45°C. This can, however, have little bearing on the problem of lymphatic flow in fever. Ōtsuka (192) studied the effects of fever following the injection of *B. Coli* in dogs and found an initial rise followed by a fall. McCarrell (166) measured the cervical and thoracic lymph flows in the dog exposed to hot air and reported a rise in the former and irregular changes in the latter. The absence of definite changes in flow from the thoracic duct are to be ascribed to technical difficulties involved in conducting away at a steady rate the lymph elaborated. This factor may also account for the failure of Beazell *et al.* (25) to find changes in lymph flow from the gastrointestinal tract at high temperatures. The present authors have made a study of lymphatic function in fever in man by means of an indirect method (4). A small amount of dye was injected intracutaneously on the forearm and the change in the surface of the stain noted after 20 minutes. The *chill* phase was associated with no change or possibly a small decrease in lymphatic function,

while in the *flush* phase a marked increase was apparent. The area stained by the dye increased in size rapidly and streamers radiated out from it.

Studies on the absorption of intradermal saline wheals have been made in patients with fever, but are difficult to interpret. Accelerated absorption has been reported in patients with febrile diseases (60, 104) but not in subjects made febrile by hot baths (60). Furthermore the accelerated absorption persists for considerable periods after apparent recovery from a febrile illness (104). It is probable therefore that the test measures some biochemical or hormonal function rather than that of the lymphatics.

XVIII. RENAL FUNCTION

Study of the volume of the circulation through the various internal organs is generally impossible in intact animals, the single exception to this rule being the kidney. Estimation of renal blood flow is possible by measurement of diodrast, inulin and other clearances, and indirect evidence of changes in blood flow through the kidneys is afforded by determination of urea clearance and more particularly the creatinine clearance.

Many years ago Mendelson (177) used a plethysmograph to study the kidney during fever in animals and observed a progressive shrinkage in the size of the kidney, apparently consequent to vasoconstriction. Fremont-Smith *et al.* (76) later demonstrated an antidiuretic effect, with cessation of urine formation, during the *chill* phase of malaria, sodoku and the reaction to intravenously injected typhoid vaccine. Clearance studies made by Smith and his coworkers (40) revealed a decrease of approximately a quarter in the volume of the renal blood flow in the *chill* phase of the febrile reaction to typhoid vaccine. All of these observations imply that the vasoconstriction observed in the skin during the *chill* phase is paralleled by a similar phenomenon in the kidneys. The *flush* phase of the reaction to typhoid vaccine is often ushered in by a profuse diuresis; the renal blood flow rapidly increases to a level considerably above normal (40, 86, 220). In addition the creatinine clearance has been found increased in dogs given typhoid vaccines (184A) and is also increased in various febrile diseases in man (93). An increase in urea clearance above normal has also been found in rheumatic fever (84) and pneumonia (85), but Farr and Abernathy (65) found it only in their younger patients. It appears therefore that the circulatory changes which occur in the kidney during an endogenous febrile reaction are similar in nature to those of the skin. They are, however, much smaller in degree.

Observations on renal blood flow in man made febrile by physical means have yielded divergent results. Byfield *et al.* (36) found no change in inulin or diodrast clearances in human subjects who developed fever in a hot atmosphere. Grant and Medes (93) reported an increased creatinine clearance in diathermy fever in dogs, while Nicholes *et al.* (184A) found a decrease; Farr and Moen (66) observed a decrease in urea clearance in human subjects in a heating cabinet. Page (193) gave diathermy over the kidneys of normal subjects and nephritic patients and noted no change in urea clearance; changes in body temperature during the course of his study are not recorded. That author and his coworkers

also reported a slight fall in urea and creatinine clearance after treatment with diathermy (30).

The above described changes in acid-base balance (*v. supra*, Sect. VIII) which occur as a consequence of fever are associated with changes in the constitution of the urine. The urine becomes more alkaline and the amount of ammonia in it decreases greatly.

XIX. GASTROINTESTINAL FUNCTION

Fever causes a lowering in volume and acidity of the gastric juice in man, according to Chang (39). Myer, Cohen and Carlson (184) induced fever in dogs by means of vaccines or with a heating cabinet and reported a marked decrease in the volume of gastric juice and in the amount of acid. This finding suggests vasoconstriction, judging by the work of Wolf and Wolff (243). On the other hand, Kuntz and Haselwood (144) showed that heating or cooling the skin of cats reflexly gave rise respectively to vasodilatation and vasoconstriction in the gastric blood vessels, particularly the small ones. It is not unlikely therefore that the circulatory changes in the stomach during a febrile episode parallel those of the skin. It should be noted, moreover, that hyperventilation severe enough to lower blood carbon dioxide concentration also reduces gastric acid secretion (33, 54), so that the above described changes may be respiratory and not vascular in origin. Petersen and Muller (198) observed that the stomach dilated during the chill phase of endogenous febrile reactions, a phenomenon difficult to explain except as a manifestation of activity of the sympathetic nervous system.

The intestine, like the stomach, exhibits reflex vasodilatation and vasoconstriction when the skin is warmed or cooled (144). Heat applied locally within the lumen of the small and large intestines increases blood flow and leads to the secretion of a large amount of intestinal juice (25). Nasset and Parry (188) found that heating a segment of isolated gut decreased absorption from its lumen; this finding suggests that blood may have been shunted away from capillaries through arteriovenous communications.

It is clear that available data on the effect of changes in temperature on gastrointestinal function are too fragmentary to permit the formulation of generalizations.

XX. HEPATIC FUNCTION

A recent attempt to study hepatic blood flow (68) in endogenous fever yielded results which cannot be interpreted with certainty. Similarly the icterus which develops in some patients given artificial fever is of obscure origin.

XXI. CEREBRAL FUNCTION

Studies on cerebral blood flow in fever are also scanty. Himwich *et al.* (118) studied arterial and jugular venous blood in a few patients given typhoid vaccine and reported a considerable increase in arteriovenous difference, a finding which suggests slowing of blood flow. These authors did not record the phase of the

febrile reaction during which their patients were studied, but it is likely that the bloods were taken during the chill phase, since clinical findings suggestive of shock were noted. Looney and Borkovic (160) made similar studies in patients treated with diathermy and found a decrease in arteriovenous oxygen difference. The pounding headache which often ushers in the *flush* phase suggests vasodilation in the brain also. It therefore appears reasonable to conclude that the changes in cerebral circulation are parallel with those which occur in the skin and kidneys.

Hyperventilation lowers the cerebrospinal fluid pressure (47), and it is possible that this phenomenon may accelerate cerebral circulation somewhat.

XXII. COMMENT

Fever induced by physical means is a simpler phenomenon than the endogenous febrile reaction, so that the mechanisms which give rise to the physiological changes of the former are fairly well established, while those underlying the latter are only partly understood. The factors directly responsible for the marked increase in metabolic activity which results in augmented heat production in fever of endogenous origin are not known, nor is it clear why a latent period occurs between the time of entry of a pyrogenic substance into the blood stream and the onset of the rise in temperature. Indeed in fever due to transient bacteremia, it has been shown that the blood is cleared of organisms by the time the *chill* phase begins (18A). The rôle of the hypothalamus must, however, be an important one in the febrile reaction, for section below it renders an animal poikilothermic and section above it causes no change in temperature regulation (20). Evidence of a more specific relation between hypothalamic function and the endogenous febrile reaction is afforded by the work of Jona (127) and of Ranson, Clark and Magoun (201). The former demonstrated that section below the hypothalamus in animals prevented the normal febrile response to the injection of pyrogenic substances, while the latter authors proved that selective destruction of portions of the hypothalamus had the same effect.

Increased metabolism induced in some manner by activity of the hypothalamus is not the only factor responsible for the rise in body temperature during the febrile reaction. The chill phenomenon plays an important part in this regard in that it results in a marked inhibition of heat dispersal through the skin and may, if associated with active shivering or with tensing of the muscles, give rise to a further increase in heat production. The mechanisms which initiate the chill reaction are not known. That the hypothalamic region contains two centers which regulate the responses to changes in body temperature has been shown by the work of Ranson and his coworkers (45, 46, 200). The more anteriorly situated center is concerned with dissipation of heat, while that which lies posteriorly controls the mechanism which effects heat conservation. It is to be presumed, therefore, that the changes in cardiorespiratory physiology which occur during the *chill* phase of the endogenous febrile reaction are consequent to a discharge of impulses from the posteriorly situated thermoregulatory center. At the same time, however, there may occur an inhibition of the normal

response of the heat dissipating center to a rise in temperature of the blood, implying a resetting of the thermostatic controls in the body at a level above normal. The latter phenomenon may have a dual origin, i.e., (1) an actual change in the temperature level at which heat dispersal has its onset and (2) the loss of vasodilating reflexes from the skin, such as are actuated when the latter is warmed directly. Both mechanisms probably play a part, but the importance of the second is suggested by the fact that Ranson (200) found that an elevation of temperature of more than 3°C . within the temperature regulatory center was necessary to activate the heat dispersal mechanisms.

The *flush* phase begins when the body temperature reaches a level which results in a discharge of sympathetic impulses from the heat dispersal center. A simultaneous inhibition of the activity of the posteriorly situated, or heat conserving center, presumably occurs. This change in hypothalamic function is apparently the consequence of elevated temperature within its substance, although the role of reflexes from the skin which is receiving arterial blood at high temperatures cannot be ruled out. Changes in blood volume and the redistribution of body water claimed by Barbour (9) to be important in temperature regulation do not appear to occur in the endogenous febrile reaction.

Once the *chill* phase is initiated, the changes in cardiorespiratory function which follow appear to be qualitatively similar to those which occur with variations in environmental temperature. Accordingly, the *flush* phase of the endogenous febrile reaction and the fever induced by physical means are much alike if certain allowances are made. In the case of patients made febrile by hot baths the cardiovascular and respiratory effects of immersion in water must be taken into account. If fever is induced by hot external temperatures, hyperventilation and perspiration are excessive, since convection, conduction and radiation are lost as mechanisms for heat dispersal. Moreover, as Kuno (143) showed, direct heating of the skin causes more perspiration than occurs when the skin temperature is raised by reflex vasodilatation. Evaporation of sweat may also be eliminated as a cooling factor, if the atmosphere surrounding the patient is saturated with water vapor, so that an additional burden is placed on respiratory mechanisms.

The changes which occur during the endogenous febrile reaction may be summarized as follows: During the *prodromal* phase no significant physiological or chemical changes can be detected. The *chill* phase is characterized by a sympathetic discharge giving rise to marked generalized vasoconstriction which causes a variable but often severe degree of circulatory stasis. The venous blood becomes deoxygenated, and the cardiac output either falls or else fails to increase in proportion to the rising oxygen consumption. Slowing of the circulation time occurs and is related to the fall in cardiac output. In some instances, however, the former may occur without the latter and in such circumstances slowed circulation time is merely a reflection of cutaneous vasoconstriction. The vasoconstriction may initially cause mild hypertension, but impairment of venous return and decreasing cardiac output result in a fall to and often well below the normal arterial blood pressure. Slowed flow and marked constriction

of the cutaneous vessels partly deprive the body of what is normally the most important mechanism for dissipating heat, so that the rise in temperature initiated by the febrile process is exaggerated. This phenomenon, and possibly also the occurrence of stasis in the respiratory center, gives rise to the marked hyperventilation of the *chill* phase of fever. Increases in respiratory rate and minute volume are largest in relation to oxygen consumption during this phase of the endogenous febrile reaction; respirations are shallow. Some degree of pulmonary congestion probably develops during the *chill* phase also and may contribute to the hyperventilation. Changes in the blood characteristic of alkalosis consequent to excessive loss of carbon dioxide uniformly occur. During the *flush* phase of the endogenous febrile reaction and in fever physically induced marked widespread vasodilatation occurs with increases in cardiac output well above normal and out of proportion to the metabolic needs of the body. Circulation times become very rapid. That arteriovenous shunts open is evidenced by arterialization of the venous blood from the extremities. The sudden vasodilatation usually results in some fall in arterial blood pressure. Hyperventilation usually diminishes in the case of the endogenous febrile reaction, but respiratory activity may still be excessive compared to body metabolism. In patients made febrile by physical means, hyperventilation, as explained above, is much greater than in individuals in the flush phase of endogenous fevers. Alkalosis occurs in both groups, however. In *defervescence* from all types of fevers all measurements of circulation and respiration return to normal over a period of some hours.

The clinical connotations of the above changes are of interest. During the *chill* phase the low skin temperature makes the patient feel cold, although the rectal temperature is rising. In fact, since the most severe chills are associated with the most marked rises in rectal temperature, patients feel coldest when they are storing the most heat. Hardy and Oppel (102) showed that in the case of direct cooling of the skin the rate of fall of skin temperature was more closely related to the sensation of cold than the absolute level; they regarded a fall of 0.004°C . per second as the threshold for perception of the sensation of cold. These considerations probably do not apply to the chill of endogenous fevers, for here the cutaneous temperature often rises after an initial fall and although it does not keep pace with the internal temperature, it may exceed the normal value. Nevertheless the patient continues to feel cold, so that a disproportion between internal and cutaneous temperatures may be responsible in part for the sensation of cold. The phenomenon of "catching a chill" and then developing a respiratory infection of some sort is a very real one to the layman. The fact that the clinical and physiological manifestations of chills may be precipitated or aggravated by exposure to cold when the subject is in the *chill* phase of a febrile reaction has been pointed out above. What probably happens in some instances is that patients, already in the *chill* phase of an infectious process but as yet with the physiological pattern of chill present only in a latent degree develop enough additional vasoconstriction upon exposure to cold to exaggerate and accelerate the physiological changes sufficiently to precipitate the clinical

manifestations. In the *flush* phase the patient feels intensely hot even though no additional change in internal temperature is detectable.

Sweating varies in the different stages of fever. In the *chill* phase a few small beads of perspiration, largely on the face, are to be seen, but in the *flush* phase of endogenous fever drenching sweats are characteristic. As pointed out above, the perspiration in fevers physically induced is usually even more marked. Sweating is the consequence of sympathetic stimulation of the sweat glands, the sympathetic impulses apparently arising in the hypothalamus. Although warming of the blood flowing through the brain is an important factor in causing sweating (78, 97), the role of impulses from the skin may predominate under some circumstances. Thus Kuno (143) has shown that skin warmed directly perspires more profusely than skin warmed reflexly. Also in the endogenous fevers sweating is slight during the *chill* phase in spite of very high internal temperatures; presumably the low, or at least less markedly elevated, cutaneous temperatures may account for this fact. On the other hand, in the *flush* phase when cutaneous temperatures are high, drenching sweats occur with no additional change in internal temperatures. The delayed onset of sweating seen in some patients at the beginning of the *flush* phase has its counterpart in the delayed onset of perspiration which occurs when the skin is heated externally after having been chilled by the external application of cold (143).

The mechanisms underlying the shivering or muscle tensing which occurs in the *chill* phase of fever have been studied by many authors; this material has been reviewed by Perera (197). When normal subjects are exposed to low environmental temperatures, shivering is said by Hardy *et al.* (101) and Swift (229) to commence when cutaneous temperature falls to approximately 20°C. However, in patients with endogenous fevers rigors occur at much higher cutaneous temperatures and here again disproportion between internal and cutaneous temperature must be considered as a possible causative factor. On the other hand, shivering at relatively high skin temperatures may be another evidence of resetting of the hypothalamic thermostatic mechanisms at a higher level than normal. Shivering and muscle tensing cause great increases in oxygen consumption, the increases associated with shivering amounting to several hundred per cent. A rise in respiratory quotient to approximately 1.0 also occurs as a consequence of increased combustion of carbohydrate and also excessive hyperventilation.

The hyperventilation of fever may possibly be a factor in the development of a variety of apparently unrelated symptoms. Thus the dizziness and, particularly in children, the convulsions which may occur at the onset of a febrile illness may be alkalotic in origin. The irritating character of the urine and perspiration sometimes noted by patients with fever may be related to the abnormal alkalinity of these secretions. Similarly the unpleasant brackish taste in the mouth which often occurs in fever may in part be a reflection of the demonstrated change in the pH of the saliva. Loss of large amounts of bicarbonate from the blood consequent to hyperventilation may reach a point at which secretion of hydrochloric acid in the stomach is greatly diminished. The

of the cutaneous vessels partly deprive the body of what is normally the most important mechanism for dissipating heat, so that the rise in temperature initiated by the febrile process is exaggerated. This phenomenon, and possibly also the occurrence of stasis in the respiratory center, gives rise to the marked hyperventilation of the *chill* phase of fever. Increases in respiratory rate and minute volume are largest in relation to oxygen consumption during this phase of the endogenous febrile reaction the; respirations are shallow. Some degree of pulmonary congestion probably develops during the *chill* phase also and may contribute to the hyperventilation. Changes in the blood characteristic of alkalosis consequent to excessive loss of carbon dioxide uniformly occur. During the *flush* phase of the endogenous febrile reaction and in fever physically induced marked widespread vasodilatation occurs with increases in cardiac output well above normal and out of proportion to the metabolic needs of the body. Circulation times become very rapid. That arteriovenous shunts open is evidenced by arterialization of the venous blood from the extremities. The sudden vasodilatation usually results in some fall in arterial blood pressure. Hyperventilation usually diminishes in the case of the endogenous febrile reaction, but respiratory activity may still be excessive compared to body metabolism. In patients made febrile by physical means, hyperventilation, as explained above, is much greater than in individuals in the flush phase of endogenous fevers. Alkalosis occurs in both groups, however. In *defervescence* from all types of fevers all measurements of circulation and respiration return to normal over a period of some hours.

The clinical connotations of the above changes are of interest. During the *chill* phase the low skin temperature makes the patient feel cold, although the rectal temperature is rising. In fact, since the most severe chills are associated with the most marked rises in rectal temperature, patients feel coldest when they are storing the most heat. Hardy and Oppel (102) showed that in the case of direct cooling of the skin the rate of fall of skin temperature was more closely related to the sensation of cold than the absolute level; they regarded a fall of 0.004°C . per second as the threshold for perception of the sensation of cold. These considerations probably do not apply to the chill of endogenous fevers, for here the cutaneous temperature often rises after an initial fall and although it does not keep pace with the internal temperature, it may exceed the normal value. Nevertheless the patient continues to feel cold, so that a disproportion between internal and cutaneous temperatures may be responsible in part for the sensation of cold. The phenomenon of "catching a chill" and then developing a respiratory infection of some sort is a very real one to the layman. The fact that the clinical and physiological manifestations of chills may be precipitated or aggravated by exposure to cold when the subject is in the *chill* phase of a febrile reaction has been pointed out above. What probably happens in some instances is that patients, already in the *chill* phase of an infectious process but as yet with the physiological pattern of chill present only in a latent degree develop enough additional vasoconstriction upon exposure to cold to exaggerate and accelerate the physiological changes sufficiently to precipitate the clinical

manifestations. In the *flush* phase the patient feels intensely hot even though no additional change in internal temperature is detectable.

Sweating varies in the different stages of fever. In the *chill* phase a few small beads of perspiration, largely on the face, are to be seen, but in the *flush* phase endogenous fever drenching sweats are characteristic. As pointed out above the perspiration in fevers physically induced is usually even more marked. Sweating is the consequence of sympathetic stimulation of the sweat glands, sympathetic impulses apparently arising in the hypothalamus. Although warming of the blood flowing through the brain is an important factor in causing sweating (78, 97), the role of impulses from the skin may predominate under some circumstances. Thus Kuno (143) has shown that skin warmed directly perspires more profusely than skin warmed reflexly. Also in the endogenous fevers sweating is slight during the *chill* phase in spite of very high internal temperatures; presumably the low, or at least less markedly elevated, cutaneous temperatures may account for this fact. On the other hand, in the *flush* phase when cutaneous temperatures are high, drenching sweats occur with no additional change in internal temperatures. The delayed onset of sweating seen in some patients at the beginning of the *flush* phase has its counterpart in the delayed onset of perspiration which occurs when the skin is heated externally after having been chilled by the external application of cold (143).

The mechanisms underlying the shivering or muscle tensing which occurs in the *chill* phase of fever have been studied by many authors; this material has been reviewed by Perera (197). When normal subjects are exposed to low environmental temperatures, shivering is said by Hardy *et al.* (101) and Swenson (229) to commence when cutaneous temperature falls to approximately 20°. However, in patients with endogenous fevers rigors occur at much higher cutaneous temperatures and here again disproportion between internal and cutaneous temperature must be considered as a possible causative factor. On the other hand, shivering at relatively high skin temperatures may be another evidence of resetting of the hypothalamic thermostatic mechanisms at a higher level than normal. Shivering and muscle tensing cause great increases in oxygen consumption, the increases associated with shivering amounting to several hundred per cent. A rise in respiratory quotient to approximately 1.0 also occurs as a consequence of increased combustion of carbohydrate and also excessive hyperventilation.

The hyperventilation of fever may possibly be a factor in the development of a variety of apparently unrelated symptoms. Thus the dizziness and, particularly in children, the convulsions which may occur at the onset of a febrile illness may be alkalotic in origin. The irritating character of the urine and perspiration sometimes noted by patients with fever may be related to the abnormal alkalinity of these secretions. Similarly the unpleasant brackish taste in the mouth which often occurs in fever may in part be a reflection of the demonstrated change in the pH of the saliva. Loss of large amounts of bicarbonate from the blood consequent to hyperventilation may reach a point at which secretion of hydrochloric acid in the stomach is greatly diminished. The

effects of abnormal gastrointestinal motility and of decreased visceral blood flow should not be disregarded, but it is not unlikely that the anorexia and nausea of fever may be related to the rapid development of hypochlorhydria secondary to hyperventilation. As fever persists, respiratory alkalosis may be counteracted by a tendency toward acidosis secondary to starvation or electrolyte loss. The marked rise in blood lactate which occurs in rigors would have the same effect. Hyperventilation in fever is associated with increased loss of water through the lungs (5) so that any tendency toward dehydration is aggravated.

A significant number of patients with febrile processes develop a shock syndrome at some time. In some instances this occurs as a consequence of depletion of salt and water during a prolonged fever, or with diarrhea or vomiting. In others the loss of appreciable amounts of blood or plasma from the circulation as a consequence of the incarceration of both these substances in a pneumonic area, or of plasma in a large abscess or phlegmon may also favor the development of shock. In still others severe anoxia may precipitate shock. However, even in the absence of all of these factors, shock may be part of the picture of infection. Thus in a severe *chill* phase following the administration of typhoid vaccine, the patient is pale, anxious, sweaty, oliguric and dyspneic and shows tachycardia and a rapidly falling arterial blood pressure; studies made at this time show a fall in venous pressure, vasoconstriction, markedly decreased cardiac output and a striking decrease in venous blood oxygen content. This state differs from that seen in other types of shock in that blood volume, oxygen consumption and rectal temperature do not fall. This syndrome is, moreover, self-limited when it occurs during the course of a reaction to typhoid vaccine. In other instances, shock appears to develop or may be exaggerated at the onset of the flush phase when sudden vasodilatation occurs.

The renal changes of fever are especially marked during the chill phase when vasoconstriction and diminished blood flow in the kidneys give rise to oliguria or anuria. Taylor and Page (232) observed hematuria and subsequent impairment of renal function in patients with kidney disorders in whom fever had been induced by means of typhoid vaccine. Such urine as may be formed in the *chill* phase usually contains albumin, shows an alkaline reaction and contains little ammonia. The *flush* phase is not infrequently ushered in by a diuresis. In addition the effects of toxic changes in the kidney and of dehydration in prolonged fevers must be borne in mind as factors making for abnormal urinary findings.

The vasomotor manifestations of fever are of particular interest in relation to the appearance of erythematous rashes. The vasoconstriction of a severe *chill* phase may cause such rashes to disappear or to become darker in hue so that at times a specific diagnostic aid may be temporarily lost. On the other hand, an extremely severe flush may also mask a macular erythema to some extent.

Congestive failure may develop or be aggravated in elderly or cardiac patients during a febrile disease of some duration. The observed increase in cardiac output in excess of the increased metabolic requirements of fever must be important in this respect.

The clinical manifestations of febrile illnesses differ to some extent from those observed during an endogenous reaction to typhoid vaccine. In the latter all phases are short and the entire episode occupies considerably less than half a day. In diseases associated with fever the duration and severity of each phase vary greatly. Thus a patient with a septic process may experience daily severe *chill* and *flush* phases, each of several hours' duration, followed by 6 or 8 hours of *defervescence*; 2 or even 3 peaks may occur daily in rare instances. On the other hand, in a patient with untreated pneumococcic pneumonia, a moderately severe *chill* phase of several hours' duration may be followed by a severe *flush* phase lasting more than a week and then a period of *defervescence* lasting a few hours or, less commonly, several days. The patient with typhoid fever apparently has several daily mild or moderate *chill* and *flush* phases with partial *defervescence* and then a prolonged *flush* phase. In spite of variations in the duration and severity of each phase of the endogenous reaction to febrile illnesses, it appears that the essential physiological patterns of each phase are preserved unless modified by anoxia, dehydration, salt loss, anemia and vitamin deficiency.

The marked strain put upon the vasomotor, cardiomotor, respiratory and sweating centers and mechanisms, together with the shifting in levels of the thermostatic controls in the hypothalamus occurring in prolonged or repeated febrile cycles such as occur in disease may account in part for the symptoms of the post-infectious state. Although the importance of biochemical and hormonal factors in this regard should not be minimized, it is reasonable to believe that the evidences of vasomotor and cardiomotor instability and of impaired control of respiration and perspiration which occur in the convalescent period are related to the above described phenomena.

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